ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 32 (O.S., Vol. XXXVI) APRIL, 1950 NUMBER 4

CONTENTS

Page

Dietary Invalidism. HENRY J. JOHN 595
Electrocardiography: Modern Trends in Instrumentation and Visual and Direct Recording Electrocardiography. F. LOWELL DUNN and WALTER E. RAHM, JR. 611
Therapeutic Considerations in Chronic Ulcerative Colitis. WALTER LINCOLN PALMER, JOSEPH B. KIRSNER and HOMER MARSHALL 627
Studies in Disorders of Muscle. II. Clinical Manifestations and Inheritance of Facioscapulohumeral Dystrophy in a Large Family. FRANK H. TYLER and F. E. STEPHENS 640
Aureomycin in Urinary Tract Infections—Preliminary Clinical Report. SEYMOUR W. RUBIN and ALBERT E. GOLDSTEIN 661
Tuberculosis in B.C.G. Vaccinated Nurses. JANET KINNEY 673
Hydrotherapy in Osteoarthritis. JOHN D. CURRENCE 682
Tularemic Pericarditis: A Report of Two Cases Including One of Constrictive Pericarditis. H. CLARKSON MEREDITH, JR. 688
The Cardioinhibitory Carotid Sinus Syndrome. ARTHUR J. DRAPER 700
Nodal Tachycardia Following Digitalis Overdosage (Stopped by Carotid Sinus Pressure): Report of Two Cases. LAWRENCE I. STELLAR 717
Case Reports:
Case of Tetanus Treated with Antitoxin and D-Tubocurarine. WILLIAM W. PRYOR and DAVID T. SMITH 728
Major Bleeding Resulting from a Single Dose of Dicumarol. JOHN J. BUTLER and DAVID F. JAMES 731
Long Term Dicumarol Therapy. RAYMOND L. RICE, JACK S. ACKERMAN and ROBERT SAICHEK 735
Neutropenia Associated with Splenomegaly and Atrophic Arthritis (Felty's Syndrome): Report of a Case in Which Splenectomy Was Performed. H. MILTON ROGERS and FRANCIS H. LANGLEY 745
Lipemia Retinalis and Xanthoma Diabeticorum in Diabetes Mellitus. AARON M. LEFKOVITS and JOSEPH M. YOUNG 755
Recovery from Addison's Disease Due to Diffuse Vascular Disease with Subsequent Development of Hypertension and Glomerulonephritis. DAVID E. SILBERMAN, L. G. ROWNTREE and HAROLD B. ORENSTEIN 760
Chloromycetin in the Treatment of Typhoid Fever. LEIF Y. JACOBSEN and RICHARD A. BRODERICK 775
Editorial—New Light on the Mechanism of the Auricular Arrhythmias 778
Reviews 784
College News Notes 790

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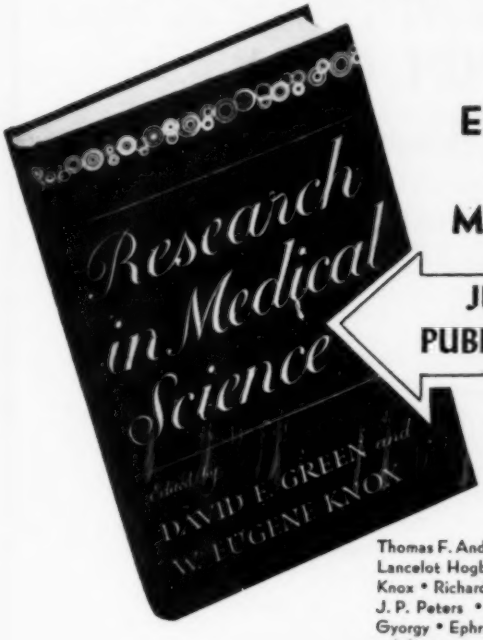

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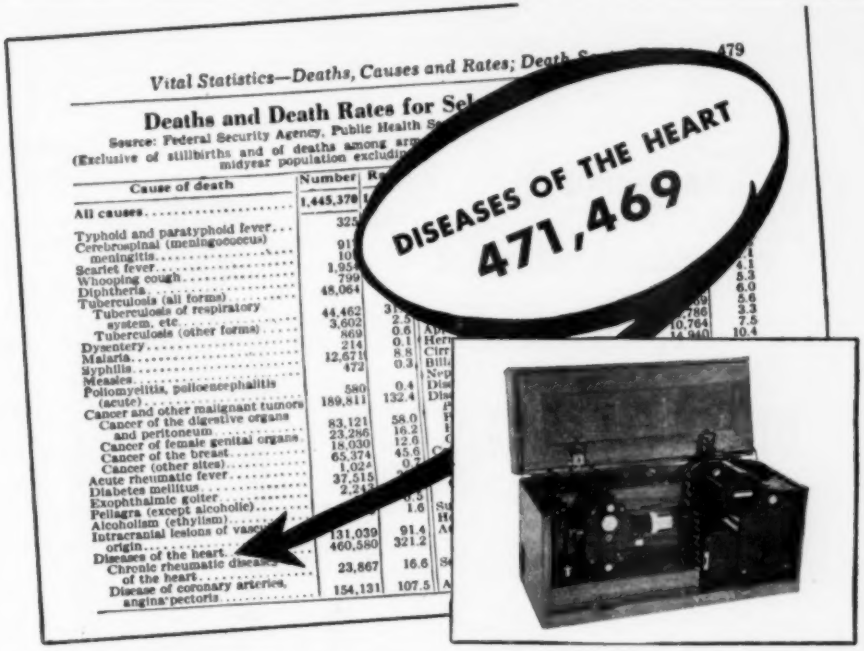

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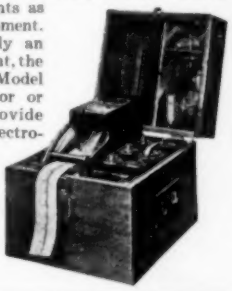

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J. ARNOLD BARGEN, M.D.,
Division of Medicine, Mayo Clinic, Rochester, Minnesota

Constipation, probably the commonest of physical complaints, may be caused by several factors, singly or combined: *1.* nervous fatigue and nervous tension; *2.* improper intake of fluid; *3.* improper dietary habits; *4.* failure to heed the call to stool; *5.* lack of exercise, and *6.* excessive use of laxatives.

It would seem logical that correction of constipation lies in the suitable adjustment of these factors.

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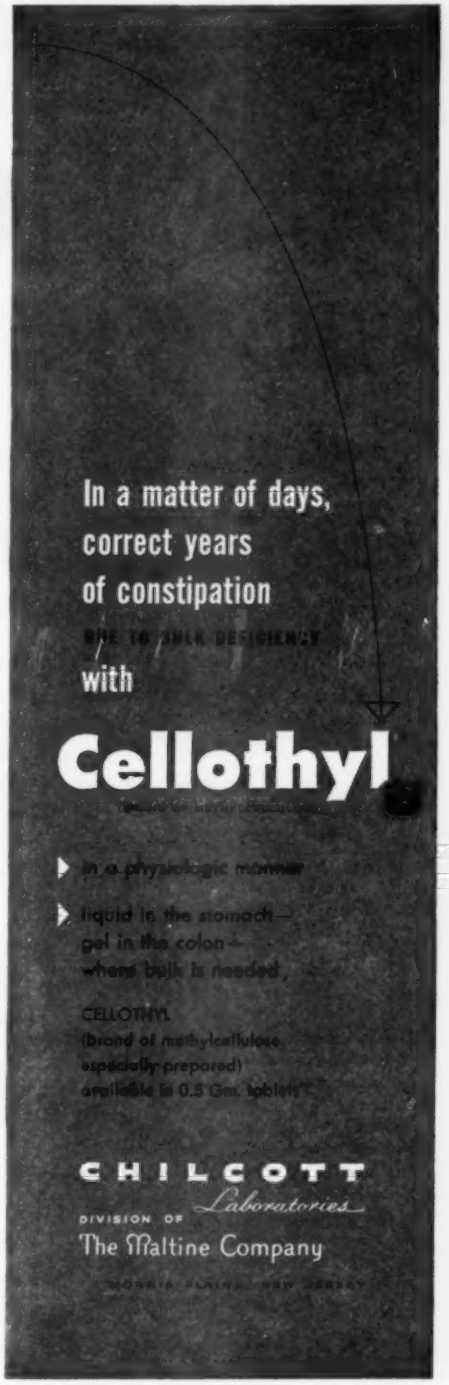

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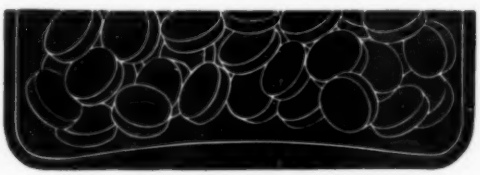

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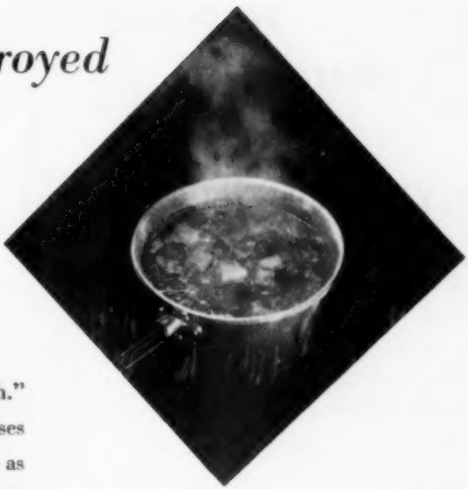

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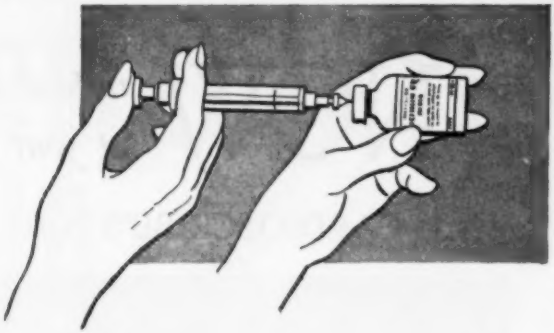

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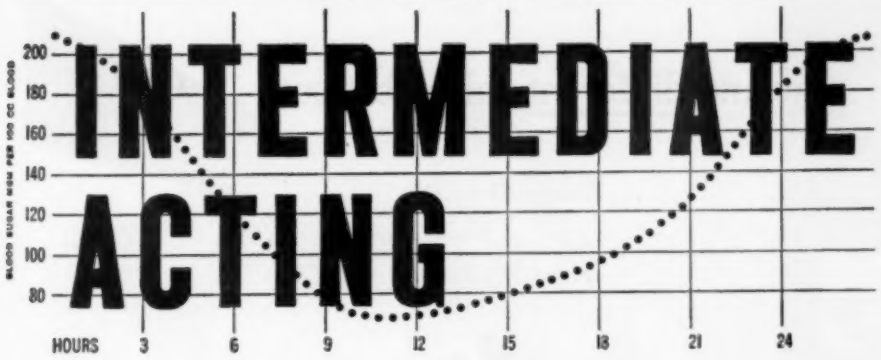

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(1) Lyon, R. A.: Am. J. Obst. & Gynec. 47: 532, 1944. (2) Cooper, M. J., and Bishkind, G. R.: J. Clin. Endocrinol. 2:703, 1942. (3) Wiesbader, H., and Filler, W.: Am. J. Obst. & Gynec. 51:75, 1946.

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Vague but persistent attacks of discomfort in the epigastrium or right upper quadrant, a bloated feeling, eructations and pyrosis are all mild forms of biliary distress. For these cases, a thorough-going course of treatment with Dehydrocholic Acid Armour may effectively control the symptoms.

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a powerful hydrocholagogue and choleretic, is prepared by the chemical oxidation of pure natural cholic acid derived from fresh ox-bile. It effects a physiologic "flushing-out" of the biliary tract by inducing a copious outflow of thin watery bile. It is of marked value in chronic gall-bladder cases, in functional hepatic insufficiency, in liver poisoning by drugs or anesthetics, in cirrhosis, and in chronic passive congestion.

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Protein	12.5 Gm.	15.8 Gm.
Fat	12.8 Gm.	8.0 Gm.
Carbohydrate	16.2 Gm.	25.5 Gm.
Calcium	0.24 Gm.	0.5 Gm.
Phosphorus	0.27 Gm.	0.4 Gm.
Iron	1.8 mg.	4.4 mg.
Vitamin A	842 I.U.	1,745 I.U.
Thiamine HCl	0.16 mg.	0.7 mg.
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Niacin	0.17 mg.	6.4 mg.
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*Egg-nog nutritive values from Bowes, A. de P., and Church, C. F.: Food Values of Portions Commonly Used. Philadelphia, 1944; fifth edition.

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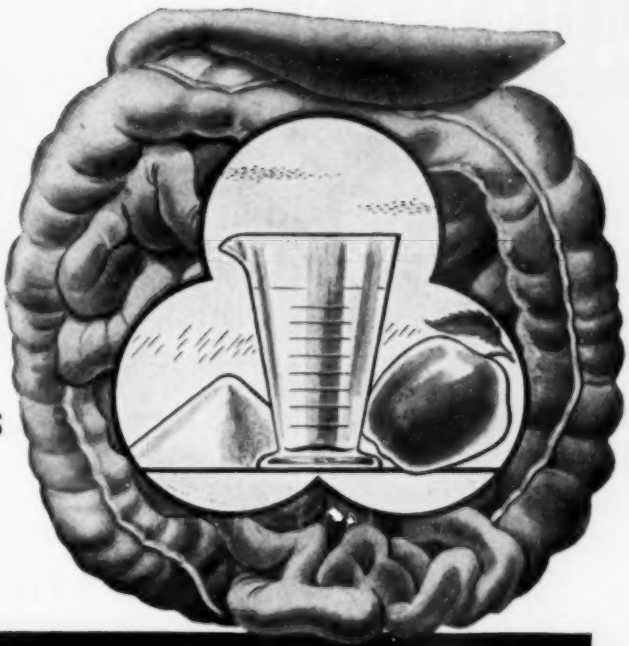

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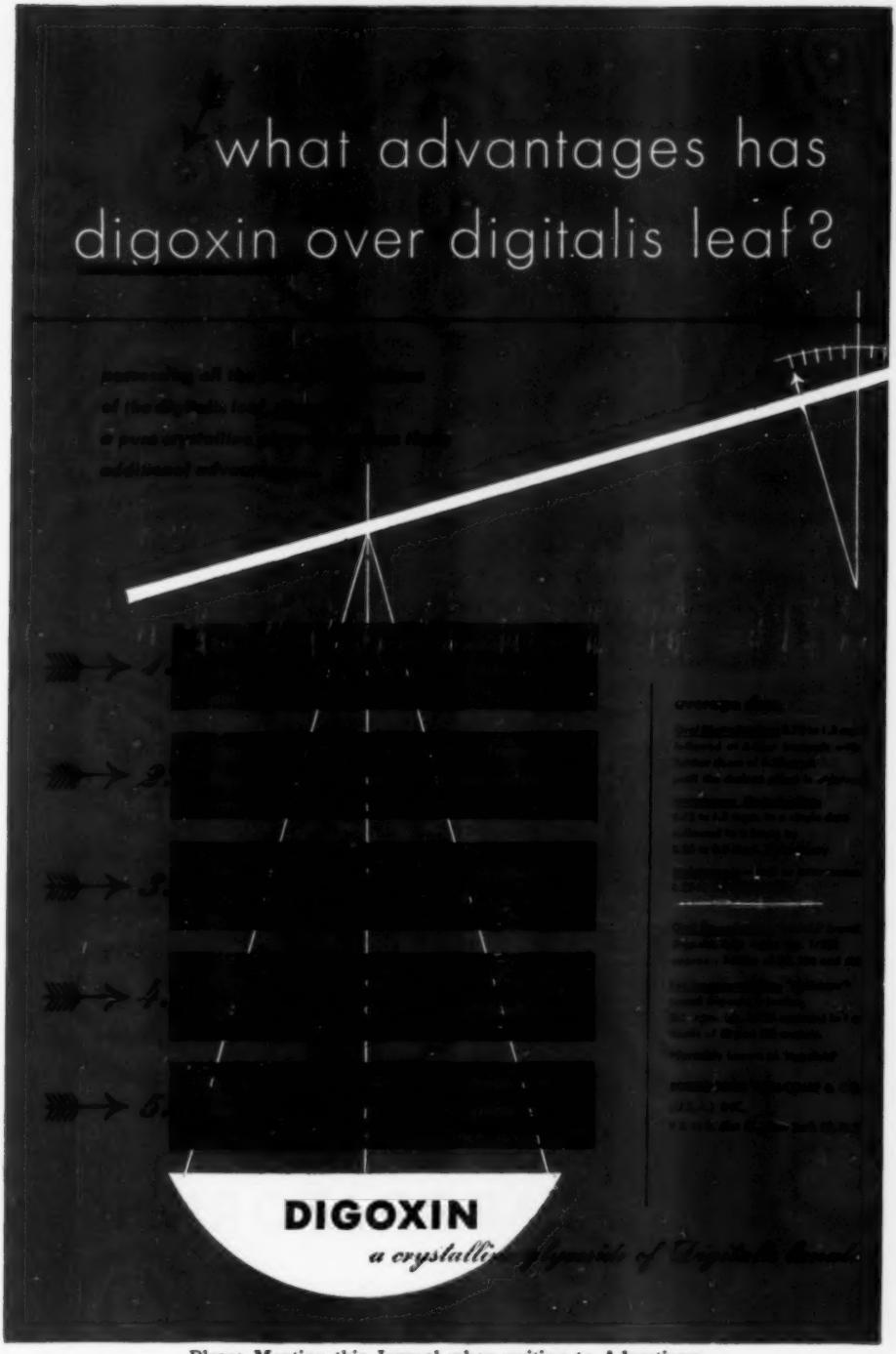
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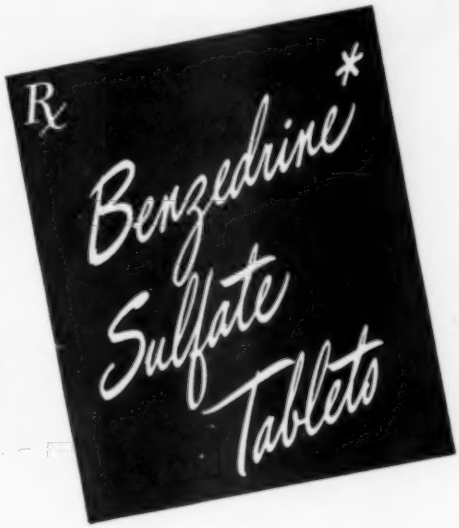

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Freed, S.C.: J.A.M.A. 133:369, 1947

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Smith, W. F.: Conn. State Med. J. 12:735 (Aug.) 1948

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*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

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Sodium restriction is an essential part of the modern management of cardiovascular failure. But, without seasoning, low sodium diets are difficult to endure. Neocurtasal, completely sodium free salt, palatably seasons all foods. Neocurtasal looks and is used like ordinary table salt. Available in convenient 2 oz. shakers and 8 oz. bottles. Constituents: Potassium chloride, ammonium chloride, potassium formate, calcium formate, magnesium citrate and starch. Potassium content 36%; chloride 39.3%; calcium 0.3%; magnesium 0.2%.

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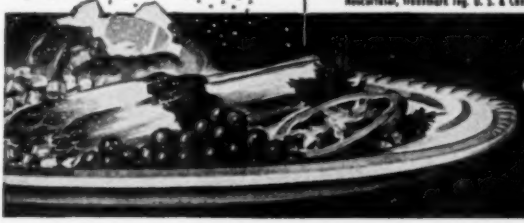

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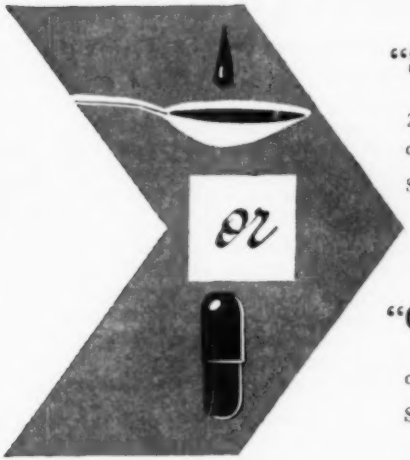
Outstanding Palatability...

Syrup Choline Dihydrogen Citrate

(*Flint*)

Continued patient acceptance of choline over prolonged periods can be assured by prescribing—



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Supplied in pints and gallons.

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containing 0.5 gram of choline dihydrogen citrate.

Supplied in bottles of 100, 500 and 1000.

"Choline (Flint)" is indicated in fatty infiltrations of the liver associated with alcoholism, infectious hepatitis, early cirrhosis, diabetes, malnutrition.

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URINARY ANTISEPTIC

Extensive clinical use of MANDELAMINE* in the management of urinary-tract infections requiring prolonged antisepsis, has established there is little or no danger that bacteria will develop resistance to this drug.

Wilhelm et al.[1] observed no instance of drug-fastness while treating 47 cases of persistent A. aerogenes infection. In some patients therapy was continued for as long as five weeks. These findings on the sustained antibacterial effectiveness of MANDELAMINE confirm the conclusions of Scudi and Duca,[2] Butt,[3] and others.

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6 Simplicity of regimen—3 or 4 tablets t.i.d.

*MANDELAMINE is the registered trademark of Nepera Chemical Co., Inc., for its brand of methenamine mandelate.

1. Wilhelm, S. F.; et al.: J.A.M.A. 141: 837 (1949).

2. Scudi, I. V., and Duca, C. J.: J. Urol. 61: 459 (1949).

3. Butt A. J.: J. Florida M. A. 35: 430 (1949).

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- **Reduced danger of crystalluria makes intensive dosages feasible with minimal hazard**
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TABLETS and PALATABS*

The *FIRST* triple-sulfa combination accepted by the Council on Pharmacy and Chemistry.

providing: SULFADIAZINE • SULFAMERAZINE • SULFAMETHAZINE

TRISULFAZINE Tablets: 0.166 Gm. (2½ gr.) each sulfonamide. For older children and adults.
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SUPPLIED: Bottles of 100, 500, and 1,000.
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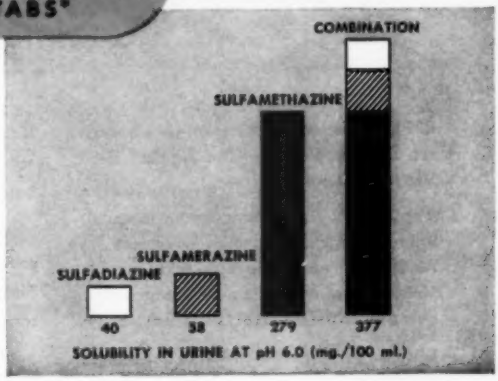

1. Flippin, H. F., and Boger, W. P.: Virginia M. Monthly 76: 56 (1949).
*Trademark of The Central Pharmacal Co.

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Here are two great Spot Tests that simplify urinalysis.

GALATEST

The simplest, fastest urine sugar test known.

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(DENCO)

For the rapid detection of Acetone in urine or in blood plasma.

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COLOR REACTION IMMEDIATELY

Combination Kit: Contains both tests, a dropper and color chart. Available at all drug-stores and surgical supply houses

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BIBLIOGRAPHY

Joslin, E. P., et al: Treatment of Diabetes Mellitus—8 Ed., Phila., Lea & Febiger, 1946—P. 241,247.

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In studies among menopausal patients:*

1. an average incidence of side effects of *less than 1%.*
2. uterine bleeding infrequent during therapy or on withdrawal.

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(Tablets . . . also Aqueous Suspension)

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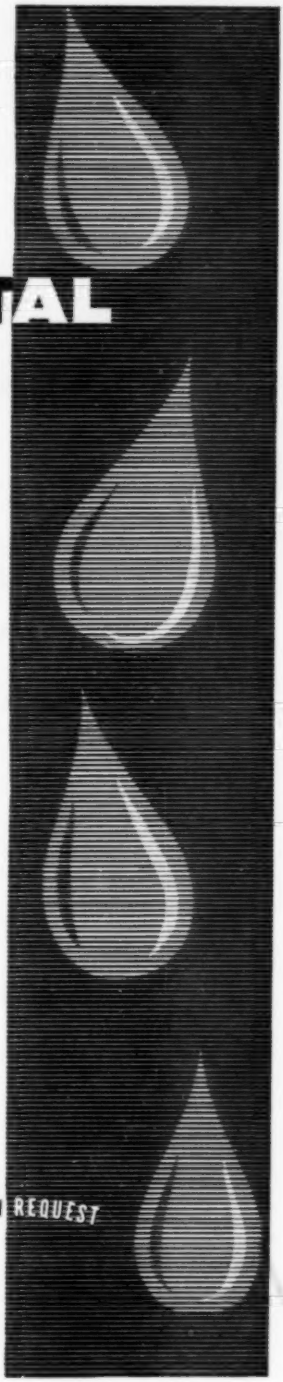

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MERCURITAL, Parker, is available on your prescription in bottles of 100 tablets. Your pharmacist has it or can obtain it for you.

References:*—*Stroud, Wm. D., and Stroud, Morris W., III, Clinics, Lippincott, June 1, 1946.*
Year Book of General Medicine, 1947.
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Wagner, Joseph A., (Steiglitz) Geriatrics, 1949.

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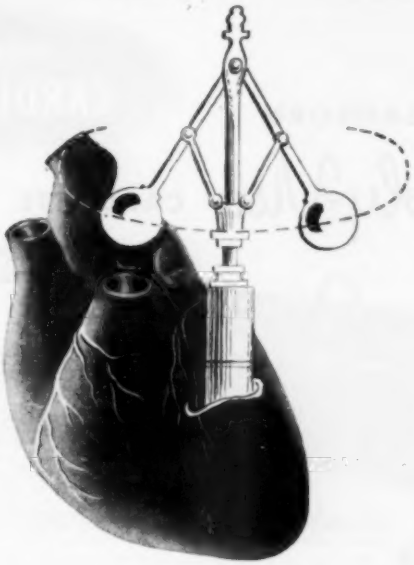

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Chief active principle of digitalis purpurea* (digitoxin)

**Not an adventitious mixture of glycosides, just the purified chief active principle.*

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CHANGE-OVER: Prescribe 0.1 or 0.2 mg. of Digitaline Nativelle to replace maintenance doses of 0.1 gm. or 0.2 gm. of whole leaf.

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This new Sanborn instrument opens the way for recording possibilities in biophysical research which until now have never been made available. Four channel direct simultaneous recording with a wide performance versatility places in the hands of the "Poly-Viso" user new tools for obtaining biophysical research information in more valuable forms and combinations.

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Design of the "Poly-Viso" is based on that of the world-wide used and accepted Viso-Cardiette described briefly below. As illustrated above, the "Poly-Viso" is completely enclosed in a mobile mahogany cabinet. It is A. C. operated throughout. *Write for the literature described in lower right corner of this page.*

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Electromanometer

For
DIRECT
Pressure
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The Sanborn Electromanometer is an instrument primarily intended for direct physiological pressure measurements, such as intra-cardiac, intra-arterial, intra-venous, pneumatic, gastro-intestinal, spinal fluid, and the like. It is used as an attachment with an electrocardiograph, the pressure curve being registered as the recording paper just as would be a 'cardiogram. While *any* 'cardiograph may be used, direct-writing instruments such as the Sanborn Viso-Cardiette, the Sanborn Poly-Viso Cardiette, or the Sanborn Direct Writing Recorder (all described at the left) are particularly well adapted for use as recorders.

The inherent natural frequency of the Sanborn Electromanometer is very high, because of its extremely low volume change as a result of pressure change. For example, 100 mms/Hg pressure change will produce a volume change of only 0.02 cubic mms, approximately.

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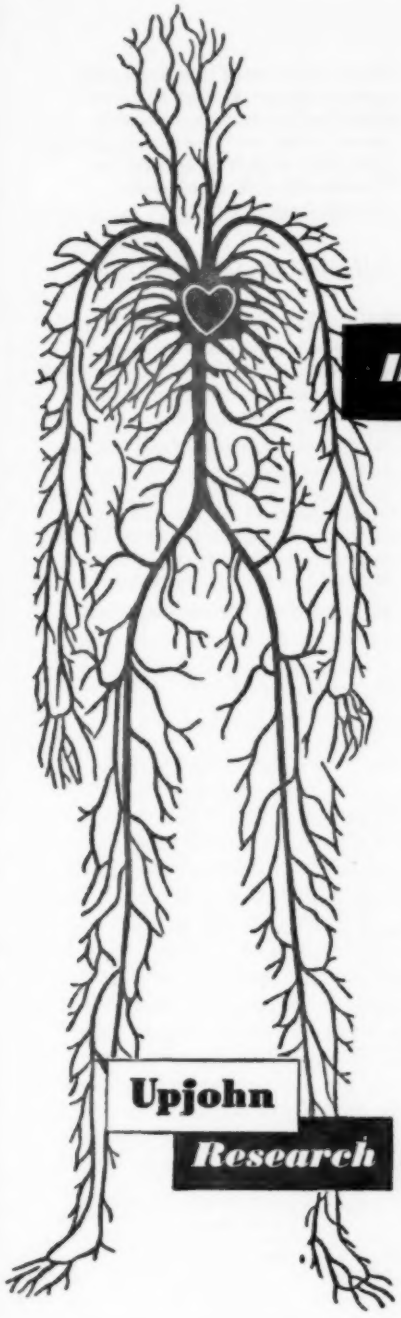

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ANNALS OF
INTERNAL MEDICINE

VOLUME 32 APRIL, 1950 NUMBER 4

DIETARY INVALIDISM *

By HENRY J. JOHN, M.D., F.A.C.P., *Cleveland, Ohio*

DIETARY invalidism is an extremely large subject, with many ramifications, and it is impossible to make a thoroughly comprehensive survey of it in a talk of this kind. Naturally, since my practice is limited to the treatment of patients with diabetes, I think first of the examples I have encountered in my own experience. I shall begin by citing a few illustrative cases and problems observed in a diabetic practice which serve to bring forth some of the aspects of dietary invalidism. Then I shall proceed to point out some of the problems that may result from dietary treatment in other diseases, and their bearing on the relationship of faulty nutrition to various symptoms and pathologic manifestations.

DIETARY INVALIDISM IN DIABETIC PRACTICE

Mistaken Diagnosis of Diabetes. The first time that my attention was centered on the problem of dietary invalidism was in 1921, not long after my return from military service in World War I. A young girl, aged 18 years, was sent to me from a distant town by her family physician because of glycosuria which he could not control, even on the most rigid diet. For over a year, it had been assumed that she had diabetes and she had been treated by a near-starvation diet, since this was before the days of insulin. She had become weaker and weaker, and had lost so much weight that she looked like a living skeleton (figure 1). She had not menstruated for over a year and was anemic. Physical examination showed no other abnormalities. A glucose tolerance test showed a normal curve (figure 2) and thus diabetes was ruled out immediately. I placed her on a generous diet, with feedings between meals, and she regained weight and strength rapidly and returned home looking like an entirely different person than when she came. Subsequent checks of the blood sugar during the following year were normal. After that, I did not see her for 27 years. This year, she dropped into my

* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 29, 1949.

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office; she is in excellent health, married and working as a cashier in a bank. During World War II she served in the WAAC.

This patient presents an extreme, but typical example of dietary invalidism. A mistaken diagnosis of diabetes mellitus based only on a finding of glycosuria caused her to become a real invalid through the starvation diet administered as treatment. She became so weak that she could hardly walk and her emaciation was extreme. The diagnosis of diabetes was unjustified, as it always is on the mere finding of sugar in the urine. This is by no means a unique case, for I have seen literally hundreds of patients who have been subjected to dietary restrictions because of such a mistaken diagnosis of diabetes. Some have undergone treatment for as long as 14 years, when no diabetes was present.

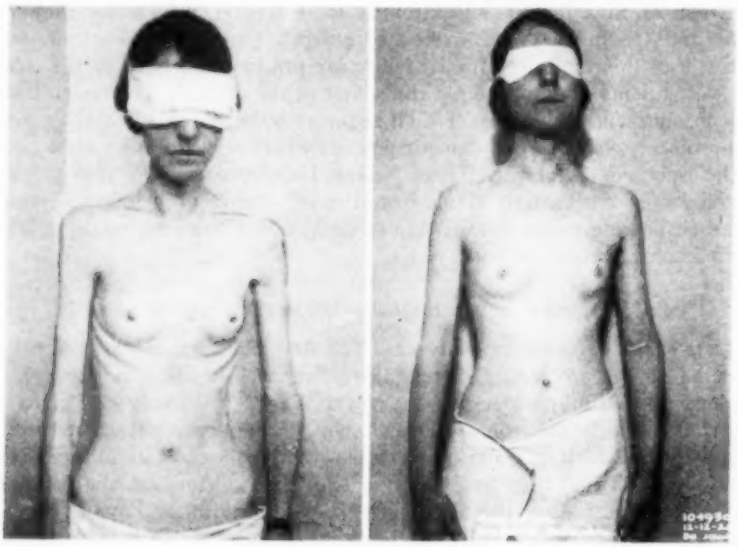

FIG. 1. Emaciation resulting from an extremely low diet imposed by her physician because of glycosuria. The patient did not have diabetes, but merely a low renal threshold for sugar.

Hyperinsulinism. A little boy, aged five years, had been having severe attacks of sweating, unconsciousness and convulsions for three years. These attacks, caused by hyperinsulinism, had become more and more severe during the six months before I saw him. Each time an attack occurred, he would be rushed to the hospital, where he was given glucose solution intravenously, and thus restored to consciousness. A blood sugar level as low as 21 mg. per cent was found in some of these attacks. He was believed to have a tumor of the pancreas and two different physicians had independently

advised an operation for removal of the tumor, or, if no tumor was found, the removal of part of the pancreas. While the parents were considering whether to have the operation performed, the child was treated by means of a high carbohydrate diet with additional feedings of carbohydrate between meals and at bedtime in an attempt to raise the blood sugar. This, as you know, is the worst possible treatment of hyperinsulinism, for with excessive quantities of carbohydrate the pancreas is being constantly stimulated and keeps pouring out more and more insulin into the circulation, thereby producing more and more severe hypoglycemia with its symptoms of unconsciousness and convulsions. This is exactly what happened in the case of this little boy.

Hyperinsulinism is of two kinds: *functional,* where there is some derangement of the insulinogenic function of the pancreas, or *anatomic,* where a tumor of the islands of Langerhans pours so much insulin into the circulation that the mechanism of nervous and hormonal control breaks down

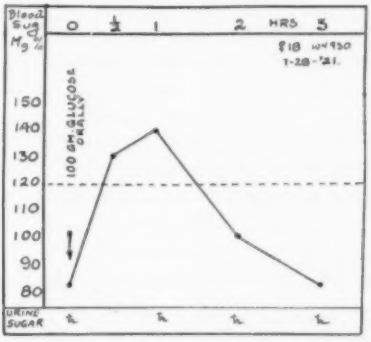

FIG. 2. Glucose tolerance in the emaciated girl shown in figure 1 which ruled out the presence of diabetes.

completely, thereby producing the marked fall of the blood sugar. In this second type, operation for removal of the tumor is indicated and is the only treatment that will correct the condition. In the functional type of hyperinsulinism, however, an operation is contraindicated, for it is not necessary and will do no permanent good, to say nothing about the tremendous surgical risk it presents.

In the case of this little boy, as in any case of hyperinsulinism, these two possibilities had to be considered. At the time I first saw him he was a dietary invalid, having been stuffed with carbohydrates all day and far into the night all the time with the result that his condition was rapidly becoming worse and the family was in despair about him.

I placed him on a restricted carbohydrate and high fat diet with feedings of ice cream, or cream and ginger ale or avocado pear between meals and at

bed time. The attacks ceased immediately, he improved, and is well today, about two and a half years later. He is nearly eight years old, living a normal life and progressing quite well in school.

In cases of hyperinsulinism, it is best always to try first the high fat, high protein and low carbohydrate diet. If the case is one of functional hyperinsulinism it will respond to such treatment. If a tumor is present, dietary treatment will not prove satisfactory, but only after such a therapeutic trial is an operation justifiable and indicated. In some cases of hyperinsulinism, I have supplemented the use of the diet with insulin, 15 to 20 units three times a day, after meals, with excellent results. Hyperinsulinism of the functional type is seen much more frequently than cases of organic origin.

In the case of hyperinsulinism just described, the use of the wrong diet certainly caused the major portion of the patient's symptoms, and thus the illness was largely one of dietary invalidism.

Food Allergy. Allergy may present another problem of dietary invalidism, especially in inexperienced hands. A child or adult may be tested and found to show reactions in the skin to as many as 10 to 15 different foods. If these tests are accepted too literally and too seriously as proof of clinical allergy, the verdict may be that these foods have to be eliminated. However, many of the indicted foods may be essential ones, and what is to take their place? It is not a question of supplying enough calories, for a quantitative deficiency may be avoided by substitutions, but the problem is that of possibly producing a serious qualitative deficiency. The vitamins can, of course, be supplied through the commercial drugs, but the mineral content of foods, which is so essential, especially to a growing child, can be supplied only by a varied diet containing adequate amounts of certain essential foods.

The question to be answered in the individual case is whether, if a skin test is positive, indicating sensitivity to a certain food, that in itself should be accepted as a definite sign that that food has to be eliminated. If there are 10 such positive tests, a tremendous problem is created, especially when the positive tests include one or more of the essential foods.

From my own experience in cases of this type, it seems evident that positive skin tests do not necessarily indicate clinical allergy. Just recently, I saw a little boy, aged nine years, who had diabetes. He looked like a child of six years of age. His mother told me that, besides having diabetes, he was also allergic to a whole series of foods, according to skin tests, and that she had had to eliminate these foods from his diet. As a result, the boy was puny, underdeveloped and undernourished. I replaced all the "forbidden" foods in his diet, and he developed no allergic reactions. With a generous and well balanced diet and good control of his diabetes, he has made good clinical progress.

Hyperthyroidism and Hyperglycemia. In severe cases of hyperthyroidism, there may be seen occasionally what might be called "unconscious"

dietary invalidism. In some cases of severe hyperthyroidism with a basal metabolic rate of plus 60 to 80 per cent, glycosuria and abnormal hyperglycemia may be observed. Such an individual has, besides severe hyperthyroidism, a disturbance of his carbohydrate metabolism which may be temporary or may remain permanently.

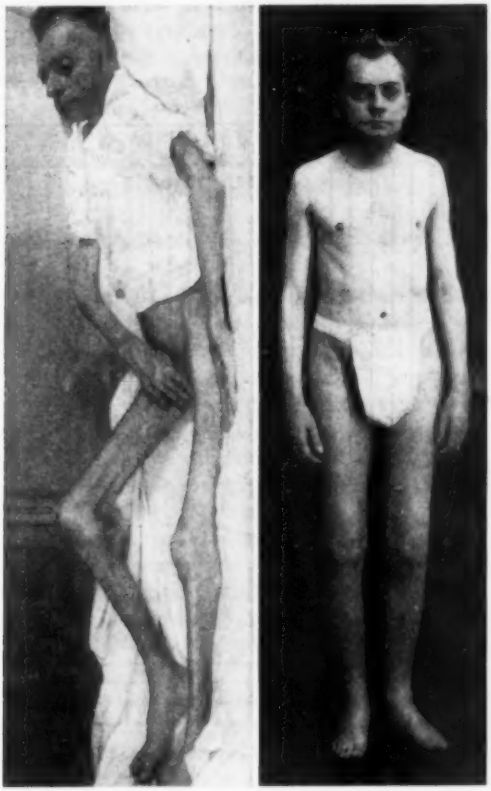

FIG. 3. An extremely emaciated man with hyperthyroidism and diabetes. The second photograph shows weight gain accomplished by proper dietary treatment.

In this type of case, if the condition has persisted for any length of time, the patient's weight has probably gone down steadily, sometimes even to the stage of extreme emaciation. Figure 3 shows such a case. This man was 33 years of age when he developed signs of hyperthyroidism about the middle of 1925. By the time he was first seen at the Cleveland Clinic, six months later, he had lost 30 pounds in weight. An adenoma of the thyroid was

found. The basal metabolic rate at that time was plus 64 per cent, the pulse rate 140 and the blood pressure 130 mm. of mercury systolic, 60 diastolic. He was placed on Lugol's solution, and ligation of the thyroid artery was carried out a few days later, followed in about a month by left lobectomy. He was sent home to recuperate in preparation for a right lobectomy. When he returned for this, nearly six months later, his weight had gone down to 86 pounds. Figure 3 represents this period. He had not been advised to take any special diet, since at the time of his first visit there was no evidence of glycosuria or hyperglycemia to indicate a disturbance in carbohydrate

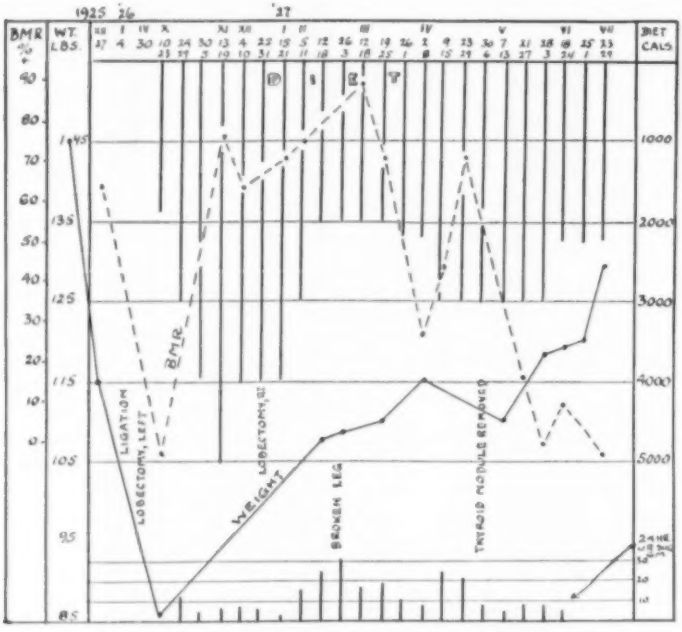

FIG. 4. A chart showing clinical data and progress in the patient shown in figure 3.

metabolism. However, a heavy glycosuria had appeared in May, 1926, while he was at home. Upon his return to the clinic in October, 1926, he had an abnormal hyperglycemia. I increased his diet to 3000 calories and a week later to 3900 and two weeks later to 5000 calories, as the chart shows (figure 4). Adequate amounts of insulin were given each day to control the hyperglycemia and to reduce the glycosuria to the minimum, which meant that he was actually utilizing the food given. The 24 hour urine sugar in grams is shown at the bottom of the chart. With this increase in food, he began to gain weight, and by the following July it had

reached 130 pounds, as shown in the second photograph of figure 3. However, his basal metabolic rate had remained high, even after the second lobectomy. A small nodule about the size of a pea was found in the thyroid scar and the basal metabolism did not return to normal until this was removed, even though he had continued to gain weight steadily.

This patient, at the time he was referred to me, presented an extreme form of dietary invalidism and was emaciated and very weak, following a weight loss of 59 pounds. Removal of the hyperactive thyroid, marked increase in the diet and administration of insulin were necessary to bring about a gain in weight which amounted to 44 pounds. This case shows that the loss of weight in hyperthyroidism should be counteracted early by appropriate increase in the diet if serious consequences are to be avoided.

The case of severe hyperthyroidism with glycosuria and hyperglycemia presents a problem that may be difficult to manage. The hyperthyroid state requires an increased food intake and the disturbed carbohydrate metabolism, or temporary diabetes, as we can call it, requires moderation in food intake.

Are these patients actually diabetic? Or is the condition a temporary one which will clear up after the thyroidectomy? It can be either. In an analysis of 9000 cases of hyperthyroidism [1] which I published in 1932, I found 6.88 per cent of the group had abnormal hyperglycemia and 19 per cent had glycosuria. All received protection during the period of increased metabolism and the final crop of permanent diabetes was 2.3 per cent. Without such protection, I feel sure this percentage would have been much higher. Even so, the figures show that the incidence of diabetes in hyperthyroidism is high. The diet cannot be restricted in amount for the hyperthyroid patient with hyperglycemia and glycosuria, for such a patient requires many more calories than he did before he developed hyperthyroidism. He must receive enough food to give him 3000 to 4500 calories a day and this must be counterbalanced with adequate insulin dosage to insure its utilization. Only in this way can serious manifestations of this type of dietary invalidism be averted.

Obesity. The most frequent and also the most serious problem of dietary invalidism with which the American medical profession has to deal is that resulting from overeating. A vast proportion of our population is or has been at some time overweight, and this constitutes one of our most serious health problems. Any physician who treats diabetic patients, as I do, is extremely conscious of this, of course, since obesity is such a prominent factor in so many cases of diabetes. Indeed, it might be said that many cases of diabetes, are, from a practical therapeutic standpoint, merely cases of dietary invalidism resulting from overeating. Often proper curtailment and balance of the intake of food is all that is necessary to control the condition.

In a recent review of 6000 cases of diabetes which I have observed personally, the maximal weight was recorded in 2970 instances. Over

half of these patients were females (52.13 per cent). Sixty-two per cent of the males and 69.5 per cent of the females were at the time of examination or had been at some time 11 to 250 per cent overweight. Hence it can be stated that obesity is a factor in a large majority of persons who develop diabetes.

Weight reduction in these cases, which means a low diet, definitely improves carbohydrate tolerance. I could cite any number of such cases, but one, in a child, will serve as an example. The patient, a girl, was aged 13, and she weighed 150 pounds. The glucose tolerance curve showed hyperglycemia. On a diet of 1400 calories her weight was reduced to 120 pounds and the carbohydrate tolerance improved immensely. A glucose tolerance test nearly a year after the first one was entirely normal. This patient, like others with similar histories, presented a question as to whether the diabetic condition, which was mild in 1934, when she was first observed, was completely corrected. The answer came in due time. Her weight, owing to disregard of her diet, again increased above 150 pounds in 1937, and the blood sugar began to rise. She married, had a miscarriage at three months in 1943, and in 1944 became a frank diabetic with a very high level of blood sugar which required insulin for its control. If she is to continue in good health, it now appears likely that she will have to use insulin and watch her diet closely the rest of her days.

Observation of many cases of this type has convinced me that hyperglycemia in the obese leads to frank diabetes if it is not counteracted by dietary restriction and weight loss. Physicians should not be misled by contrary teachings that hyperglycemia in the obese is not diabetes, but just a temporary disturbance of the carbohydrate metabolism which can be safely disregarded.

Other factors, such as heredity, degenerative changes in the circulatory system and infections also are involved in the development of diabetes, but in many cases the evidence indicates that these factors, without the added strain of overeating, might have been compensated adequately by the insulinogenic apparatus. In other instances, it appears that overeating is alone responsible for a breakdown of function of the islets of Langerhans. Overeating, particularly of carbohydrates, causes overstimulation of the pancreas and when this is continued over long periods, there is eventual degeneration of its function. In mild cases the disability may be overcome and adequately controlled by proper diet and reduction in weight. In others, the damage is permanent and irreversible.

Obesity also is a factor in many other diseases, especially those afflicting the middle-aged and elderly. Degenerative diseases, such as heart disease, hypertension and other circulatory disorders, renal insufficiency, liver disease, and perhaps even cancer, are all related, in part, at least, to indiscretions in eating and drinking and the presence of obesity. The symptoms, in many cases, particularly in heart disease and hypertension, show marked improvement when the diet is curtailed and obesity disappears.

The only way to counteract obesity in the diabetic or any one else, is by a restriction of food intake. In many patients, particularly in some women, the restriction must be severe in order to effect a loss of weight. It may be necessary to limit the diet to 900 calories, or even less, to accomplish any reduction. This is often difficult for the patient and creates at times a psychologic problem which may interfere with continuance or proper adherence to treatment. Those who have overeaten all their lives are naturally self-indulgent, and rigid discipline and breaking of habits of long standing create a serious problem for them.

It has been my experience, however, that the results are much better and the psychologic difficulties much less if the physician is extremely firm about the matter and places the patient, from the outset, on a diet low enough to yield satisfactory results. A moderate reduction in diet makes a patient feel miserable and abused and rarely produces any effective weight loss. This discourages the patient and he feels that this deprivation is of no avail. It also undermines his confidence in his physician and makes coöperation with him more difficult. To restrict the diet moderately at first and then increase the restrictions as time goes on is to administer treatment backward, in my estimation. If calories are cut drastically at the beginning, the patient begins almost immediately to lose weight, he feels a sense of accomplishment and well being and this stimulates him to continue treatment. Furthermore, in this way, dieting is really easier for him, since severe curtailment at first shrinks the stomach and intestines, and thus diminishes the constant feeling of hunger that is present when there is only slight or moderate decrease in food intake. A stringent diet at the start helps the patient to develop a habit of real moderation in eating, for even though the diet may be increased later, some moderation will have to be continued indefinitely.

When diets are administered in this way, they seldom bring about the feeling of dietary invalidism that may be engendered by less radical methods. Of course, it is important that the patient remain under medical supervision while he or she is on an extremely strict diet. Emphasis must be placed on adequate intake of protein and other essential food factors when very low diets are administered.

Complication of Dietary Routine. As in the case of the diabetic patient or any other who is obese, the dietary regimen must be strict and radical enough to be effective, but in the treatment of diabetes particularly, and perhaps in dietary treatment generally, the routine has often been made much too complicated and difficult for the average patient to follow. Dietary treatment may be strict and still be relatively simple to carry out from day to day.

Before insulin was available, the dietetic routine for patients with severe diabetes was extremely hard. The diet had to be reduced to the amount which that patient's endogenous insulin could utilize. This led, of course, to undernutrition and dietary invalidism. However, only by this means could the lives of these patients be prolonged. When insulin was intro-

duced, this rigid dieting no longer was necessary, and gradually diabetic diets were increased more and more, until now they are virtually normal diets, in fact, they often allow more food than many of us ordinarily consume.

Although the diets have been increased greatly, a simplification of the dietary program has lagged far behind this progress. Patients were, and still are, instructed in the calculation, weighing, planning, etc., of their diet, with the result that they usually develop a fixed idea that their diet is considerably different from that of the rest of the family. Yet they eat the same bread, the same potatoes, the same meat, the same vegetables and the same fruit. In reality, the only difference, in most cases, is that they eliminate sugar, pastry and soft drinks; the remainder of the food is the same as that of other members of the family. Why then create this psychologic hazard and feeling of invalidism by making the diet seem so complex? It certainly is not desirable from the standpoint of coöperation of the patient in the control of diabetes, and frequently it is harmful. Psychologic invalidism resulting from a complicated routine in many instances is just as crippling as real dietary invalidism.

A typical situation of the past, and in too many instances even at present, as exemplified in a hypothetical case, may be described as follows: Let us suppose the patient to be an old Italian woman, aged 70 years, who weighs 96 pounds and is found to have diabetes. She is placed in the hospital and receives a special diet and insulin. The blood sugar soon falls to normal and the dosage of insulin is closely adjusted so that she is fairly well controlled. Now the doctor comes in and tells her about diabetes, about all the dire things that may happen to a diabetic, such as acidosis, coma, blindness, gangrene, leg amputation, etc. As a result, the poor old woman is "scared to death." What if these things should happen to her? Thus she is "conditioned" for the next chapter of her inquisition, performed by the dietitian. The patient listens to a long dissertation on foods, their contents, and hears much about the carbohydrates, the proteins, the fat and the calories. All this is completely new to her and although she listens as though her life depended on it (which she has been led to believe it does) she has little or no understanding or comprehension of what it is all about.

She receives sheets and sheets of diet instructions, sample menus, charts of food values, tables of grams and calories, and she has no idea whether a gram is the same thing as a calorie or whether protein is a poison or carbohydrate a manna. If the instruction does not continue long enough, over a period of several days, with much repetition,—and it usually does not, for the dietitians in our hospitals are quite busy and have many other things to do,—the whole matter remains a colossal and frightening puzzle to the old woman. Dietitians and others who instruct diabetic patients tend sometimes to forget that they themselves had years of training in dietetics or nursing, with gradual instruction in the chemistry of foods, physiology, etc., where one subject dovetails into the next and thus makes a continuing background for the understanding of such special therapeutic diets. The

poor patient we are talking about hasn't even finished the sixth grade, in fact often has but little understanding of English, for she had to start work in her early teens to help provide for the family, then married, reared children and worked hard all her life, and now, at 70, she is sick with what she knows may be a mortal disease, and hence is completely frightened, depressed and confused. The dietary instructions which seem so simple to the well educated dietitian are to her completely bewildering. She listens to the routine without understanding and becomes completely discouraged.

About this time, when the dietitian realizes that she has not made any headway with her scientific instructions, she usually gives up and simply writes out a few menus for the patient to follow, which probably begin something like this:

Breakfast—0.5 grapefruit
3 tbsp. breakfast food with cream, 30 c.c.
3 strips bacon and one egg
2 pieces of toast, 3 by 3 inches
Coffee

The patient never in her life has eaten that much breakfast. Her regular routine for the past 50 to 60 years has been one or two pieces of bread or toast and coffee. She knows also that the Pope in Rome eats the same thing. Now, however, she is sick with diabetes and this big breakfast is a prescription and she has been frightened into believing that she must eat exactly as directed. Well, at least the two pieces of toast are familiar to her. But the diet says that they must be 3 by 3 inches. So she has to buy a ruler and measure the slices, and then cut off a quarter of an inch all around. The rest of the meal she has to choke down, but the dietitian said she had to eat all, so she does. The other meals are accordingly difficult, or more so, for her.

Yet, such a patient is usually on a relatively simple 2000 calorie diet, which is virtually normal. But as this has been outlined to her, it looks like a mountain. She does the best she can with it, but often this is not good enough. Often these poor people are put on a low diet, say 1600 calories, in order to keep them sugar-free. Such a diet is not adequate for their bodily needs. And even though the diet is cut very low, they may still show glycosuria, in which case either their insulin is increased or their diet decreased and hence their weight goes down and they become true dietary invalids. I have seen quite a few patients of this type. To keep diabetic patients sugar-free has become a fetish with many doctors who do not understand normal physiology. There are many patients who have a low renal threshold for sugar and these patients will show glycosuria when the blood sugar is normal or below normal and others have a high renal threshold and will show no glycosuria when the blood sugar is high, even 300 to 380 mg. per cent, or more. The patient with a low renal threshold is certainly "out of luck" when he happens to be treated by one of these "sugar-free en-

thusiasts," as was shown in the first case reported here. Just recently, I saw an old man, whose protamine zinc insulin had been increased to 125 units in the morning and 100 units in the evening, to get him "sugar-free." Even so, this was not accomplished, yet he required only 60 units of insulin daily for good control of his diabetes.

To return to the old Italian woman. Does she need such a stereotyped diet? Does she have to cut away the outside of the bread slice so it will be exactly 3 by 3 inches? Does she have to eat the breakfast food or the egg for breakfast which she has never been in the habit of eating? Do we have to interrupt her normal way of living and make the remainder of her life miserable? Do we have to crowd in the extra calories just to fit the insulin dosage decreed for her? Isn't it much more sensible to tell her to eat in her own way and reduce the insulin to fit the amount of food consumed? The chances are about nine out of ten that if she is allowed to eat according to her own desires, insulin may not be necessary at all. Do we have to make this poor old soul a "dietary invalid" just to fit her into a groove of our own making?

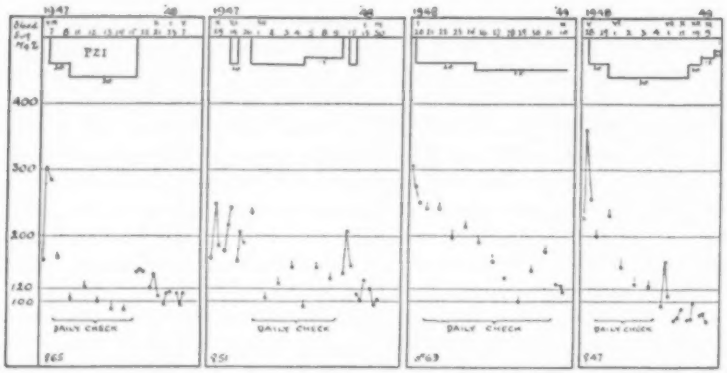

FIG. 5. Chart showing satisfactory clinical progress of patients on a liberal regimen of treatment for diabetes.

My own experience [2] proves that this is not necessary. For over two and a half years now I have tried a simplification of the diabetic routine, letting patients choose their own food, asking them only to eat in moderation and to eliminate sugar, soft drinks and pastries. Such a simplification of the program has made them feel comfortable, has eliminated any thought of invalidism and has resulted in satisfactory progress in controlling the diabetic condition (figure 5). As a matter of fact, this type of regimen has worked out much more satisfactorily than I expected, and the evidence so far indicates that with this simplification of the dietary instructions and restrictions, the patients limit themselves to a lower intake than is allowed on many weighed and calculated diets on which they feel deprived.

Other Types of Malnutrition and Dietary Invalidism

Some of the general aspects of quantitative and qualitative dietary deficiencies have been alluded to in connection with the discussion of problems encountered in a diabetic practice, but there are many other patients with bizarre symptoms and some with fairly well defined syndromes which are caused by diets deficient in caloric content or in some essential food factor. It is impossible, in a paper of this kind, to describe in detail these numerous manifestations of faulty nutrition, but it seems worthwhile to allude to a few of the more common problems.

Dietary deficiencies are usually interrelated, so when there is a caloric insufficiency, there is likely also to be a deficiency in one or more essential vitamins or minerals, a fact which accounts for the great variety of symptoms that are seen in such cases. Apparently an intrinsic constitutional factor also may be involved in the individual case, so that the utilization of certain food elements is impaired, to complicate the picture further.

Certain types of dietary deficiencies are confined largely to certain geographical areas in which, owing to poverty and poor living conditions, the diet of a large group in the population is deficient or lacking in certain types of foods. An example of this is to be found in certain sections of the south, where too many people live largely on a diet of corn grits and sow belly. Pellagra, nutritional anemia and various other syndromes and symptoms observed in this group have been studied by Spies and his associates, whose investigations have added much to the general knowledge of the effect of faulty diet on the general health.

Spies [8] has pointed out that nutritional deficiencies are to be suspected as a cause of symptoms in persons whose diets have been inadequate; in those whose utilization and absorption of nutrients seems impaired; in chronic alcoholics and in persons with dietary idiosyncrasies. Sometimes repeated questioning is necessary to elicit the possible rôle of a faulty diet in the patient's illness, for many patients with bizarre eating habits who eliminate many essential foods from their diet are not at all aware that they are not eating a normal diet. It is often difficult, too, to find out whether alcoholism may be a factor in a suspected dietary deficiency, because many who drink habitually are not aware of the large quantity of alcohol they are consuming, since they do not (at least in their own estimation) become really drunk.

The chronic alcoholic who has a dietary deficiency may or may not be emaciated. In extreme cases, little food is taken and the calories are furnished almost entirely by the alcohol. In such instances, there is almost sure to be a vitamin B deficiency, which may even lead to peripheral neuritis. Another factor which enters into faulty nutrition in cases of chronic alcoholism is liver damage caused by the excessive drinking, which precludes normal functioning of the liver, interference with glycogen storage and many other functions necessary for good health.

In families of low or modest income, chronic alcoholism in one or both parents may result in malnutrition and dietary deficiencies in the children, who are not provided with a proper diet.

It is well, in taking the histories of patients, to find out whether or not they have been on special diets of any kind, for often such treatment is responsible for the development of real nutritional deficiencies. Sometimes this is the fault of the physician who has been in charge, in that the diet has not been properly balanced, or the doctor's instructions have been insufficiently explicit, or he has not exercised proper supervision of the patient. At other times, nutritional deficiencies developing following dietary treatment are the fault of the patient, who has not followed the diet according to instructions and has excluded some items which seemed to him unimportant, or has confined his food to just a few of the items allowed, or has not kept in touch with his physician, or has continued the special diet after the physician believes he has returned to a normal food intake.

Psychologic factors elicited in the history may give the clue to the presence of a suspected dietary factor in illness, since depressed mental states and emotional difficulties may lead either to overeating or undereating or abnormal craving or dislike for certain kinds of food, which may result in a one-sided diet. Often those who prepare their own food and eat alone get into very faulty dietary habits which may lead to malnutrition and specific dietary deficiencies. The middle-aged or elderly woman who lives alone often falls into this category, for it seems too much trouble to bother to prepare a proper meal just for herself. The result is that she eats cereals or sandwiches and as time goes on, she becomes more and more tired, and the preparation of food seems to be an even greater task. Thus her diet becomes more and more deficient, and often she develops gastrointestinal symptoms which lead her to believe certain foods are disagreeing with her, and she restricts her diet still more. This type of patient is likely to have a variety of symptoms, digestive, rheumatic, nervous, dermatologic or ophthalmic. Young women who cut down their food to save expense or who diet, without proper supervision, to lose weight, often develop symptoms that are attributable to lack of calories, protein, vitamins or minerals and are easy prey for infections, particularly tuberculosis.

The symptoms of malnutrition or of a specific dietary deficiency may be referred to any part or system in the body and may be present in combinations of endless variety. Gastrointestinal symptoms, skin eruptions, eye difficulties, nervousness, psychic depression, fatigue, irritability, anemia and even organic nerve lesions are common findings in the various nutritional disorders. Any patient whose symptoms cannot be attributed to a specific cause should be carefully questioned regarding his or her diet, for often a dietary history furnishes the clue to the entire illness. Even when some definite disease is present, a faulty diet may be a factor aggravating or complicating the clinical picture.

Justifiable Invalidism Resulting from Therapeutic Diets. Many restric-

tions in diet which are imposed by the physician in the treatment of certain conditions in themselves produce a hardship on the patient which might be regarded as a form of dietary invalidism; but these are entirely justifiable in view of the results they achieve. Allusion has already been made to the difficulties imposed in the past by diets for diabetics, and the measures that may be taken to decrease these. The stringency of the reduction diet for obesity imposes on some patients a difficulty that they regard, from a practical standpoint, as invalidism, and yet such stringency must be insisted upon if satisfactory results are to be produced. In some cases of allergy, virtual dietary invalidism is created by the proscription of numerous foods.

Although it must be admitted that some dietary treatment is severe and imposes definite hardship on the patient which constitutes a form of invalidism, it must be emphasized that the psychologic attitude of the patient is often a prominent factor in such invalidism. The physician should do everything possible to simplify the routine in any therapeutic diet and to make it as liberal and varied and hence as attractive as it can be made for the patient. The physician can also do much to counteract an adverse psychologic attitude and feeling of deprivation by persuading the patient to coöperate, by emphasizing his responsibility in the matter, and by impressing on him the beneficial effects of the diet, rather than its hardships.

Gastric and Duodenal Ulcers. Many patients with gastric and duodenal ulcers have been dietary invalids, partaking of frequent milk feedings and talking alkalies between. No man can work efficiently if he has to be constantly ulcer-conscious and follow a prescribed dietary and medication routine that is constantly interrupting his activity. It is interesting to note that during the past 50 years doctors have recommended at least 46 different kinds of diet and 108 different drugs, vitamins, sex hormones, etc., in treatment of peptic ulcer.

Although an enormous quantity of clinical and experimental data have accumulated during the past two or three decades on nutritional diseases and the relation of diet to health, it seems probable that much more will be learned in the future. Dietary treatment is already important in many diseases, and is rapidly being extended to various forms of heart disease, and other conditions in which previously it has not been regarded as significant. A thorough knowledge of nutrition, of the effects of faulty or deficient diets, of dietary therapy and of the planning of dietary routines for patients is essential to the modern physician.

Summary

Dietary invalidism is a frequent problem encountered almost daily in the practice of any physician, and is, of course, particularly evident in the group of patients who consult a specialist in diabetes. Dietary invalidism, which has great variety owing to overeating, undereating, constitutional factors in the individual, and so on, is sometimes produced by the patient's own

faulty eating habits and sometimes by dietary treatment administered by a physician. In the latter category, some cases are justifiable, since stringent dietary restrictions may be required to correct a serious pathologic condition. Unjustifiable cases of dietary invalidism usually result from errors in diagnosis, from an inadequate evaluation of the situation, from improperly planned and balanced therapeutic diets, or from inadequacy of the measures taken to assure that the full utilization of such a diet actually occurs. Administration of dietary treatment calls for constant vigilance and thorough understanding of the physiologic, pathologic and psychologic factors which comprise the medical problem.

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ELECTROCARDIOGRAPHY: MODERN TRENDS IN INSTRUMENTATION AND VISUAL AND DIRECT RECORDING ELECTRO-CARDIOGRAPHY *

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Thomas Lewis in the introduction to his "Mechanism and Graphic Registration of the Heart Beat" emphasized that scientific advancement depends upon the development of suitable instrumentation.[1] In the pioneer days of Einthoven and Lewis the problem was to design and construct an instrument which would permit a study of what has become electrocardiography. Einthoven's contribution was to adapt the tight string instrument originated by Ader for submarine telegraphic purposes to the requirements of cardiac electrophysiology.[2] Einthoven pointed out the marked superiority of the new string galvanometer to the older capillary electrometer—the time saved in making records and the avoidance of the complicated corrections necessary because of the poor frequency response of the electrometer.[3, 4, 5] Following Einthoven many modifications of the string galvanometer have been made. Some of the earlier ones are illustrated by Wiggers.[6] In 1926 Williams completed a comprehensive report on the design and construction of the string galvanometer including the construction details of several models which were widely used in electrocardiography until the more recent enthusiasm for portability.[7]

At the time of Williams' comprehensive studies the string galvanometer was in the unique position of being the only instrument with adequate sensitivity for recording small and rapidly varying currents. As a result many string galvanometers were built for special purposes including some with strings as short as 2 millimeters which would respond to frequencies as high as 10,000 cycles per second. Such an instrument, a twelve channel oscillograph, was made by Western Electric and called the Minagraph. The vacuum tube was in commercial production at that time but the circuits were poorly understood and the tubes were unreliable and low in amplification. In the early 20's several investigators had constructed vacuum tube amplifiers and had recorded electrocardiograms.[8] Forbes, Davis, and Emerson in 1930 pointed out that string galvanometers in use at that time were far too slow in frequency response to give even an approximately true recording of the time relationships of the action currents in nerves.[9] They used

* Received for publication April 30, 1949.
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The authors wish to express their appreciation for funds received from the Life Insurance Medical Research Fund.

a special short string galvanometer designed by Williams and a vacuum tube amplifier apparently designed by Bell Laboratories. Forbes and his associates at that time stressed the superior qualities of the cathode ray tube in spite of the poor brilliance and large luminous spot available in these early Braun tubes. The tremendous advances in circuit design and vacuum tube construction have eliminated the shortlived supremacy of the string galvanometer and today its use is confined largely to clinical electrocardiography. In the research laboratory and industry suitable instrumentation is accomplished more effectively and economically by use of electron tube assemblies.

Until very recently improvements in electrocardiographs have been primarily in portability and the assumptions seem quite general that (1) present day instruments are as good as some of the earlier and larger models, (2) that they are as good as necessary for clinical use, or (3) that there is no need for more accurate equipment in electrocardiography. This is somewhat the reverse of the attitude of Lewis in his emphasis on the importance of instrumentation. The marked progress of the last decade in recording rapidly varying small currents makes available for electrocardiography new refinements in precision and adaptability. Our studies would indicate that Lewis' emphasis on instrumentation is still pertinent.

In clinical electrocardiography, except for gains in portability and the lag screen electrocardiograph of Asher and Hoecker, there have been very few successful attempts to utilize the many advantages that electronic circuits offer.[10] Electrocardiographic instrumentation has proceeded in the direction of duplication of the records of the string galvanometer. The situation may be somewhat analogous to C. F. Kettering's humorous remarks about the problems of designing Diesel engines. First, he said, they tried to build them like marine engines—massive in weight and slow in speed. This didn't work and next they tried to build them like automobile engines—light weight and high speed. They weren't successful until they built them like Diesel engines, with the well known results. Imitation of the string galvanometer occurs in (1) the use of the wide line record, (2) the use of shadowgraph illumination, (3) the use of optical systems for magnification and photography, (4) making the coördinate system at the time of the recording, (5) the use of the 0.04 second time interval and (6) the use of string galvanometer records as standard. The wide line record which is 2 mm. or more in width is necessitated with the string galvanometer because of the high magnification (about 600 diameters) necessary to record the minute movements of the string. The wide line conceals 60 cycle pickup and fine detail and is not used by choice in other types of recording when accuracy is required. The shadowgraph type of illumination in which the whole field is illuminated and the record appears as a shadow makes definite limitation in the amount of contrast between the illuminated portion and the shadow. This loss is easily noted if one attempts to record a 60 cycle per second variation at 1 to 2 cm. amplitude. The peaks are hard to locate

and the lines almost invisible. Much greater contrast was obtained in earlier electrocardiographs when the direct current arc was used as a source of illumination. The Western Union zirconium crater arc lamps would in all probability offer illumination comparable to the arc light since the color temperature of the crater is much higher than possible with filament lamps.[11] Many of the portable amplifier electrocardiographs could use a spot of light with a much greater brilliancy of the record, and several decades ago one well known electrocardiograph did use a spot of light. Later this instrument was changed to the shadowgraph type of record.

Optical systems are essential for the string galvanometer and to these are attached the delays and expenses of preparing a photographic record. It is only recently that any attempts have been made to introduce direct recording with its many potential advantages to be discussed in more detail later. The disadvantages of having the coördinate system the same color or density as the record reduces clearness although amplifier models permit using recording paper in which the coördinates are reduced in intensity or of a different color. The argument is made by some electrocardiographers that the coördinate system must be made at the time the record is made in order to ensure accuracy because of possible speed change in the driving mechanism or varying shrinkage of the paper during photographic processing. Such objections have lost their value with the widespread use of constant speed motors which have been reliably tested. The twenty-fifth second time interval goes back to the early tuning fork timers and today a 0.1 second interval can be obtained accurately and would be simpler for interpolation.

The assumption is general that the string galvanometer is standard although, so far as we are aware, this is based upon data obtained prior to the development of electronic circuits. With the present day refinements in cathode ray recording and the use of circuits with known frequency characteristics this assumption requires further verification. The extensive use of the string galvanometer record as the standard rests, we believe, upon the fact that earlier methods of determining frequency response were much more limited than those available today. As a result there are inadequate data available on what frequency characteristics are necessary for proper electrocardiographic recording. *It has been easier to design instruments so that they approximated the form of the string galvanometer record rather than to make a survey of the frequency problem involved.* This method is not sound instrumentation practice and many of us will recall differences between string galvanometer and amplifier type records such as notching of the QRS and differences in the slope of the ST segment. Johnston's excellent summary of available data on the frequency response necessary for electrocardiography brings out this lack of adequate data for effective design.[12] This will be discussed in more detail later.

So many gadgets are being introduced into medicine that many of us are becoming mere button pushers and switch wigglers. The electrocardio-

graph is beyond the stage where it is used only by an expert. One does not need to see many records sent in for diagnosis to realize that operation is not uniformly excellent. One of us recalls the personal satisfaction of writing the diagnosis on one record that was sent in for a possible coronary problem, "Weak B Battery," and later receiving a satisfactory record. Two solutions to this difficulty suggest themselves: (1) the electrocardiographer can become sufficiently familiar with instrumentation so that he knows how to take proper records and can recognize equipment that is not operating properly, or (2) the design of what the industrialist calls, when his client is not around, "foolproof equipment." The simplicity of control and reliability developed in the electronics industry, partly as a product of the recent War, implies that electronic tube electrocardiographs can be made more foolproof. For example the frequency response is fairly constant for the life of an amplifier and the skin contact resistance does not affect the frequency response over a wide range. With the string galvanometer high skin resistance requires slackening of the string to give a standard deflection and this alters the frequency response of the string. Experience shows that this is too common an error.

Some of the possible advantages which may be derived from the use of electronic tube circuits are (1) direct recording electrocardiography, (2) visual and cathode ray electrocardiography, (3) relay operation, and (4) remote recording. These will be discussed in more detail.

The success of direct recording in electroencephalography prompted us about eight years ago to apply the method to electrocardiography. Briefly the electroencephalograph consists of a suitable amplifier which increases the few millionths of a volt obtained from the scalp electrodes until sufficient power is obtained to operate a recording mechanism. Except for the Brush Crystovibrograph the recorder consists of a magnet and moving coil resembling a loudspeaker. The moving coil is held in the magnetic field by a spring so that it can move in or out according to the current flowing in the moving coil from the amplifier. This movement is transmitted to a writing lever which traces the record on a moving paper strip. Attempts to use the electroencephalograph for electrocardiography showed marked deficiencies in the records. Q and S waves were reduced or absent; the ST segments slanted abnormally; the heights of the various elements were abnormal: and the transitions were smoothed out. These deficiencies were due to a lack of high frequency response because of the inertia of the writing arm, the mass of the moving coil, and the weakness of the spring mechanism, and to the lack of adequate low frequency response because of the amplifier design —the coupling condensers were too small in capacity. Figure 1 illustrates the frequency response of a standard design of electroencephalograph and shows graphically the amplitude of the deflections obtained at different frequencies when the input is from a signal generator producing a constant sine wave voltage at the various frequencies noted in the abscissae. The amplitude begins to rise rapidly at about 0.8 cycle per second, reaches a

maximum at about 3 cycles per second, and begins to drop at about 20 cycles per second reaching a very low level at 60 cycles. Thus a signal at 60 cycles per second must be about 10 times stronger than a signal at 10 cycles per second to give the same response. This range of frequency response, although suitable for electroencephalography, is inadequate for electrocardiography.

The few tests with the electroencephalograph raised the question as to what frequency response was necessary for accurate electrocardiography. Johnston summarized much of the useful data available on "the frequency response necessary to produce standard lead records without distortion."

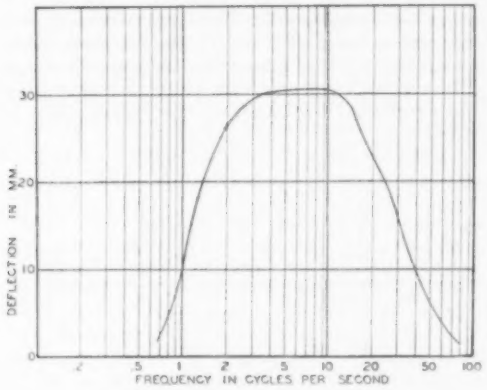

FIG. 1. The response curve of an electroencephalograph constructed by Rahm. The abscissa is the frequency in cycles per second. The ordinate is the amplitude of response to a constant voltage at the frequency in the abscissa.

For a string galvanometer, "if the deflection time is 0.02 second or less and if critical damping is present the rapid changes will be recorded without distortion." Also, "electrocardiograms are complex non-periodic waves and an extensive analysis of the frequencies involved has never been carried out; nevertheless it has been found that an amplifier which responds uniformly from frequencies of approximately 1 cycle per second up to 50 cycles per second will, when driving a properly designed oscillograph, yield curves identical with those taken on a string galvanometer." He also quotes Schwartzschild and Kissin that in order to record the low frequencies without significant distortion the time constant should be two seconds. These three specifications of frequency are not easily converted from one to another and do not correlate. The time constant is difficult to determine in complex circuits and relates to the amplifier whereas the frequency response desired is the overall response of the electrocardiograph. Cossor pointed

out that the low frequency response was an important factor in electrocardiography and set a value much lower than that in Johnston's summary.[12] Because of the lack of published data the frequency response curves were determined on eight electrocardiographs in clinical use.

Method. Through the courtesy of Omaha physicians we obtained eight portable electrocardiographs for test. These were considered by them and us to be in good condition and were in clinical use. Because of the low frequencies required for the study it was necessary to construct a sine wave generator to provide a calibrated voltage as input at frequencies from 0.1 cycle to 10,000 per second. The waveform and the amplitude of the generator was monitored by visual observation of a cathode ray tube during the tests. The output resistance of the signal generator could be varied. This was not critical for the amplifier types of electrocardiographs and in most of the observations was 1000 ohms. However in the case of the string galvanometers this shunt resistance is of critical importance since it determines the tension of the string and we used 2500 ohms. Records were made by the electrocardiographs under test at a series of frequencies and constant voltage and the amplitudes measured. These were then plotted with the frequencies as abscissae (figure 2). Three string galvanometers and five amplifier type photographic recording electrocardiographs were tested.

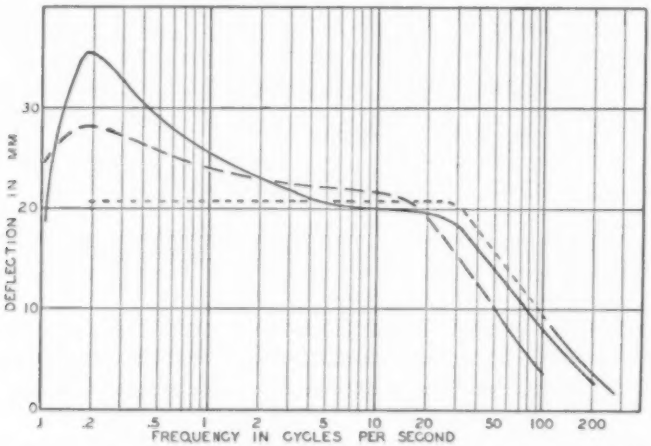

FIG. 2. Comprises three response curves of eight portable photographic electrocardiographs in clinical use. Solid line is average of 3 amplifier instruments, long dash line is average of 2 amplifier electrocardiographs, and the short dash line is the average of 3 string electrocardiographs. Johnston recommended that an amplifier which responds uniformly from frequencies of approximately 1 cycle per second to 50 cycles will, when driving a proper oscillograph, yield curves identical to those taken on a string galvanometer (see text). The Council on Physical Medicine of the American Medical Association (J. A. M. A. 134: 455, 1947) "Report on minimum requirements for acceptable electrocardiographs," states in paragraph 3, "The amplitude response of the instrument to 1 millivolt peak sinusoidal voltage variation up to 15 cycles per second shall not fall below 90 per cent, and up to 40 cycles shall not fall below 50 per cent of the square wave response to equivalent voltage variations. The amplitude response of the instrument to 1 millivolt peak sinusoidal voltage variation up to 300 cycles per second shall not exceed 100 per cent of the square response to equivalent voltage variations."

Figure 2 shows that the frequency responses obtained all have a similar general appearance. The results obtained for each type of instrument were sufficiently alike so that graphical averages were made and the individual observations are not recorded. One can infer that both amplifier types would give an increased amplitude to the T wave and other slow frequency variations as compared with the string galvanometer. All types show a beginning reduction in response below 40 cycles per second. These curves do not satisfy Johnston's specifications as noted previously. Thomas Lewis in his discussion on obtaining standard electrocardiograms sets somewhat more strict specifications than Johnston and then states, "this condition is more than fulfilled by the instrument here described, of which the natural frequency is approximately 100 to 200 cycles per second under ordinary working conditions." [13] The results recorded in figure 2 raised the question as to what the electrocardiogram looked like when recorded by a method which did give uniform response over a wide frequency range. Such equipment can be made available today in the form of a cathode ray tube and a direct coupled amplifier. Records were made on 10 normal male adults with such equipment and comparison records made on some of the machines tested above.

Method. A direct coupled amplifier was constructed of conventional type. It was single-ended and no condensers were used except in the power supply of the last stage. Separate batteries were used for each stage except the last, and each stage was separately shielded. A shielded cage was used for the subject to give clean records entirely free from interference. The output of the amplifier was connected directly to the electrostatic deflection plates of a 5 inch cathode ray tube. Photographs were made on 6 cm. PMC bromide paper using an F 4.5 lens and uniform speed camera. The stability of the assembly was excellent except on a few days of high humidity and a constant input voltage would give constant deflections for periods of 10 to 30 minutes. The intensity of the cathode ray tube was such that a four inch sine wave at 20,000 cycles per second could be sharply photographed with the relatively slow emulsion paper used.

As is well known electrocardiograms produced by direct coupled amplifiers and cathode ray tubes show the same general features recorded by the types of clinical electrocardiographs tested in figure 2. The small size and brilliancy of the spot of light in the modern cathode ray tube produced a record that was admirably suited for the study of detail. Close study of the 10 records in comparison with string and amplifier oscillograph records showed definite differences in detail. Heights of Q, R, S, and T vary up to 10 to 20 per cent between the direct coupled records and those of the electrocardiographs tested in figure 2. The P waves showed finer detail not further evaluated. These differences can be inferred from a comparison of the frequency response curve of the direct coupled amplifier assembly (figure 3) and those in figure 2. Due to the fact that individual clinical electrocardiographs differed in response it did not appear useful to make any tabular comparison but it was apparent that the present frequency charac-

teristic used in clinical electrocardiography did produce definite distortions in recording. The direct coupled studies implied the desirability of a greater range of uniform frequency response than those stated by Johnston, and in current clinical use.

The data in figures 2 and 3 together with Johnston's recommendations were considered as sufficient to specify the characteristics for the design of a portable direct recording electrocardiograph. It is fortunate for the direct recording engineer that the frequency range used in clinical electrocardiography is as limited as it is. The low frequency response can be obtained easily but the high frequency response introduces technical difficulties. It is easy to design an amplifier with the desired response but the upper limit is set by the recording mechanism involving a problem in size, magnetization, length of lever arm, size of moving coil, stiffness of the spring diaphragm.

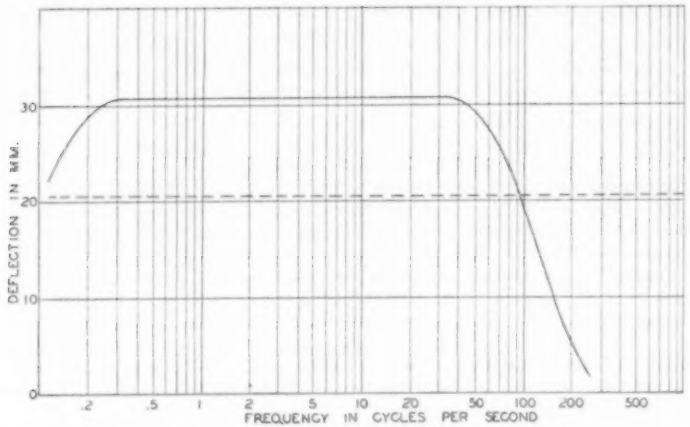

FIG. 3. The solid line is the response curve of the direct recording electrocardiograph. The dash line is the response curve of the direct coupled cathode ray assembly.

Figure 3 illustrates the response of recorder and amplifier as constructed by one of us (R). Recently this response has been improved by further redesign but the many factors involved would seem to make it extremely difficult to make recorders that will give an amplitude and a frequency response that is much superior to the types of instruments tested in figure 2. A considerable improvement could be made if the amplitude was reduced one-half, i.e. 1 millivolt equal to 0.5 cm., but there is no indication that this would be acceptable to the clinician. There are many advocates today for 1 millivolt equal to 2 cm. Some improvement in frequency response can be made by redesigning the amplifier so that it selectively amplifies some of the higher frequencies, i.e. what is known as a tuned amplifier.

Since the writing lever pivots on an axle the vertical movement of the

record is along an arc. This represents a departure from the string galvanometer type of record in which the long optical beam is used but is a type of record that has been accepted in the physiological laboratory and in many of the industries. The coördinate paper can be easily ruled to conform to this curvature so that no arc error is introduced, although most timing measurements in clinical electrocardiography are made along the base line. Attempts to produce a vertical and linear movement of the recording pen have been by (1) the use of pantograph assemblies, (2) by sharply curving the paper and using a knife edge stylus instead of a point, and (3) by curving the paper so that it conforms to the arc error with the stylus in line with the writing arm. Pantograph assemblies are apt to develop loose motion and reduce the high frequency response. The knife edge method does not give as clean records in our experience and the third method is mechanically complicated in its present forms. If the arc type of record is acceptable to the clinician it certainly provides the most rugged type of construction.

Various types of recording paper were tried. Ink produces records of high legibility but the long tube used to convey the ink to the tip requires conscientious care to prevent clogging. The Western Union Teledeltos paper used for facsimile recording gives erratic legibility with smoking and sputtering and lacks high contrast between the record and the background. Wax coated papers give brilliant records with very light stylus pressures especially when a heated stylus is used. Attempts to use this paper in a general hospital over a period of six months were unsatisfactory. The records scratch easily and are affected by room temperatures in summer, and by filing pressure. In spite of this wax paper because of its cheapness provides an excellent method for taking long records cheaply or for temporary data such as in surveys and the like and should have a definite place in electrocardiograph recording. Wax coated papers have been improved by using various plastic coatings but none of these in our experience has the durability of the photograph when properly processed, or ink. One of us has modified a thermochemical paper in which a heated stylus produces a chemical reduction with deposition of a black metallic element. This gives a record of high visibility and a permanence the same as ink or photography. The thermal stability of the paper is such that high temperatures are necessary to produce the reaction so that no blackening of the paper occurs even on exposure to direct sunlight for weeks. Figure 4 illustrates the completed electrocardiograph and figure 5 is a sample record.

The direct recording electrocardiograph illustrated in figure 4 with the frequency response curve in figure 3 produces records of the same general quality of those clinical portable electrocardiographs in current use. The addition of a lead marker recorder, and a selector switch which permits selection of the standard limb leads, the augmented extremity leads of Goldberger, the CL, CR, CF, and V leads is a further step towards simplicity and reliability in operation. In our earlier studies it was hoped that a re-

cording mechanism could be designed which would be definitely superior in frequency response but if portability is an essential feature it has not proved practical up to the present to construct a magnetic type of direct recorder that combined any considerable extension of upper frequency response over current clinical electrocardiography without reducing the amplitude of the deflection or increasing the present weight of the instrument (30 pounds).

FIG. 4. Direct recording electrocardiograph with cover removed.

However the direct recorder has features which originally prompted its design, (1) immediately visible record and elimination of the photographic process, (2) great reduction in cost of operation, and (3) constancy of frequency response. The immediate visibility of the record is an obvious advantage. In addition to being able to make electrocardiographic diagnosis in the clinic or at the bedside without delay, the electrocardiographer has the opportunity critically to inspect the record, correct the presence of artefacts due to position, breathing, tension, or he can study the record during various functional tests. Data can be written on the record with pen or pencil at the time of the observation. Three tape speeds are provided,

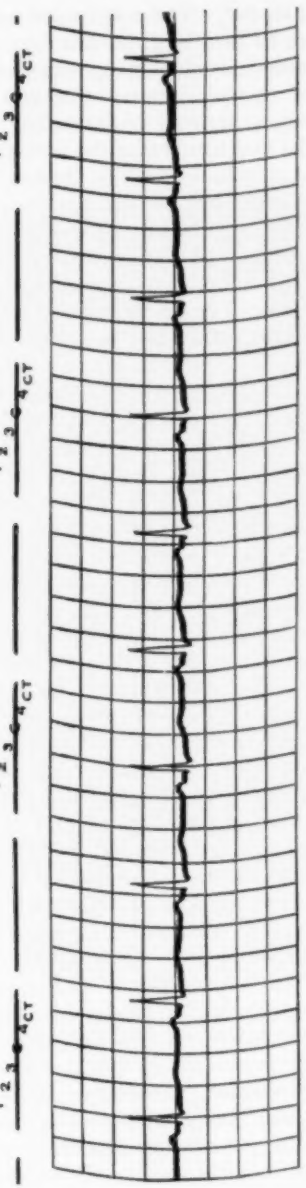

FIG. 5. Recording made by direct recording electrocardiograph using a thermochemical paper.

1.25, 2.50, and 5 cm. per second. The easy demonstration of differences in the electrocardiogram due to breathing, posture, etc., has been of value in student teaching and should aid in developing a more widespread knowledge of the variations in the normal electrocardiogram. Most electrocardiographic diagnosis is based on the study of only a few beats in each lead and the direct recorder permits and encourages the making of longer records.

The use of electronic circuits to amplify the heart action potentials to such a level that a relay could be operated has been applied in numerous ways including lights to flash the heart beat and x-ray photography of the heart at various phases of its cycle. These applications in the past have at times been unreliable in operation. Because of the great increase in relay applications and electron control in the machine tool industry, aviation, and communications, these circuits can now be made to operate reliably and without technical skill.

During the period when the electrocardiograph was a bulky piece of equipment including a heavy magnet, arc light and long optical path, hospitals were fitted with conduit systems by which the patient in the ward could be connected to the instrument and the feeble heart action currents transmitted to the "heart station." Most of these systems were a continual source of difficulty because often stray currents were picked up in the wiring and conduit which were as great or greater then the heart currents to be recorded. Probably this difficulty was an important factor in the development of the portable electrocardiograph. The heart station idea may have some desirable features today and with the use of electronic amplifier circuits it becomes feasible. By the use of a small portable and inexpensive preamplifier at the bedside the heart action currents are amplified to such a level that stray currents in the conduction wires become insignificant. The amplified signal is conducted to the heart station where more bulky or specialized apparatus can be used. Preamplifiers can be connected to a number of patients who are under electrocardiographic observation and at the heart station proper switching permits the operator to observe or record the trace as desired. Modern shielded cable can be obtained at only a fraction of the cost of the older cables used and with marked superiority.

From our studies current clinical electrocardiographs produce definite distortions in recording. These distortions are probably greater today than when more bulky apparatus was used. The use of a proper amplifier and a cathode ray tube will provide essentially distortionless recording. The superiority in recording is apparent to anyone who has seen the small brilliant spots of light of the modern cathode ray tube. The widespread use of cathode ray equipment demonstrates that it can be made at low cost. Assemblies can be made compact. Multilead channels are easily possible since single tubes have been made which will record simultaneously 24 records. Multilead recording is accepted practice in electroencephalography and the assumption is permissible that a more widespread application in electrocardiography would simplify rather than complicate interpretations.

Cathode ray tube assemblies have the advantage that they can be used for visual or for photographic observation. We have no definite data to prove that a linear frequency response would be an advantage in the field of electrocardiography, but have demonstrated definite distortions in present day records. From an instrumentation standpoint the situation is somewhat the

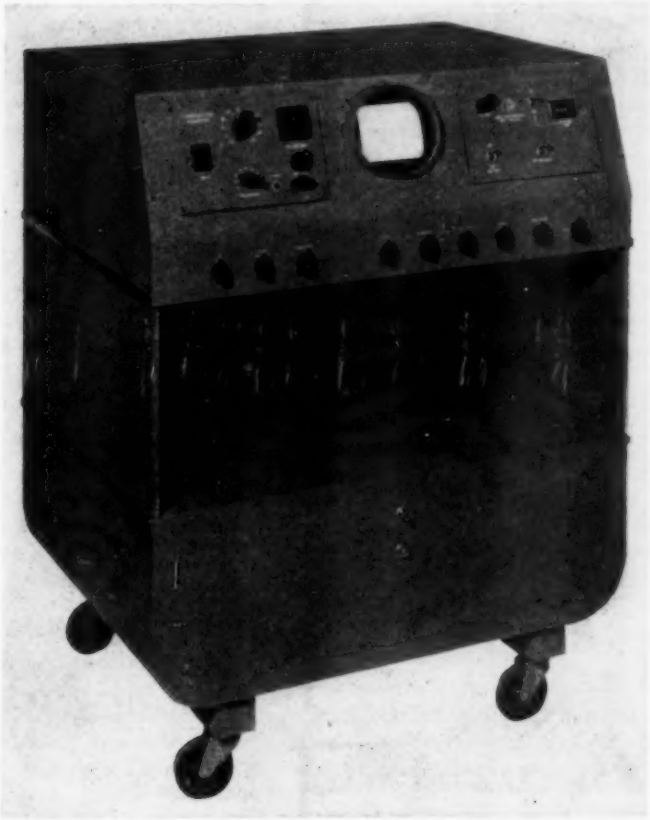

FIG. 6. Cardiograph monitor. The open space is for insertion of camera, extra amplifiers, or other accessory equipment.

reverse of that in the time of Einthoven. Then the problem was to develop a new instrument which would do the best job possible and certainly the string galvanometer was a supreme achievement in concept and in the refinements of mechanical construction. Today the electrocardiographer can have an accuracy in recording hitherto unattainable, if he will demand it.

FIG. 7. Recording by cardiograph monitor. The up spikes are spaced at 0.1 second intervals and can be varied in amplitude or changed to down spikes.

Figure 6 illustrates a cathode ray electrocardiograph which has been used in the past three years for visual observation during surgery, at the bedside, and for demonstrations to students of variations in the electrocardiogram. The cathode ray tube has a phosphor with long persistence so that the trace remains visible for a short time. An accurate sweep circuit is included which moves the beam from left to right at the uniform rate, the speed being adjustable. The effect is that of writing the electrocardiogram across the tube, and the first part of the trace fades as the sweep flies back and retraces the next row of beats. For best observation the sweep is adjusted so that two or three systoles occur during a single sweep. Another cathode ray tube with camera assembly is built into the cabinet so that photographic records can be made at any time. A timing device superposes small spikes on the record at 0.1 second intervals. This is adjustable in height and brilliance and makes accurate measurement of the components of the trace easy. Figure 7 is a sample record.

The combination of the cardiograph monitor and direct recording electrocardiograph has been tried for making electrocardiographic surveys of small groups and is rapid and economical. The method provides a rapid technic for elimination of normals but provides a quick recognition of abnormal records so that more detailed studies can be made at the time.

Summary

1. Many of the easily available potentialities of electronic devices have not been utilized in electrocardiography, and until very recently the trend has been to imitate the recordings of the string galvanometer.

2. Frequency characteristics of eight clinical portable electrocardiographs were determined and compared with recommended frequency standards and with recordings obtained from a direct coupled cathode ray electrocardiograph.

3. Some of the problems of design of a direct writing electrocardiograph have been discussed.

4. A comparison between clinical electrocardiograms and a direct coupled cathode ray electrocardiograph was made using 10 normal males. Restrictions of frequency response of the clinical electrocardiographs tested resulted in definite distortions of the electrocardiogram components and loss of fine detail.

5. Modern developments in cathode ray tube and electronic devices permit the assembly of multichannel electrocardiographs of high fidelity at low cost both for visual observation or photographic recording.

6. Electronic devices permit the use of a "heart station" by utilizing a small preamplifier at the bedside where the heart currents are amplified to such a level that stray currents in the conducting systems become insignificant.

7. A cathode ray electrocardiograph is illustrated and its value discussed

from the standpoint of fidelity, visual and photographic observations, and use in conjunction with a direct recording electrocardiograph for making electrocardiographic surveys.

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THERAPEUTIC CONSIDERATIONS IN CHRONIC ULCERATIVE COLITIS *

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Bargen [1] has very properly emphasized the importance of differentiating the various types of colitis since precise diagnosis is essential for proper treatment. The present discussion is limited to the thrombo-ulcerative form, using Bargen's terminology. The diagnosis need not be reviewed here except to point out the great importance of proctoscopy because the rectum is involved in 95 per cent of the patients. The roentgen evidence is less conclusive because when the process is limited to the rectum and sigmoid, as it frequently is, or when the descending colon is involved to a minimal degree only, the examination is normal. Aside from the proctoscopic demonstration of a diffusely granular, friable, edematous rectal mucosa, there is no pathognomonic sign of the disease.

Etiology

The various theories of etiology have been ably reviewed by Ginsberg and Ivy.[2] Bargen considers the disease to be of streptococcal origin. We are convinced of two things: (1) that the process is a true inflammation in which infection of some sort does play a very considerable rôle, and (2) that emotional factors, if not primary, are of great importance in the course and treatment.[3]

Differential Diagnosis

The most important conditions to exclude are bacillary and amebic dysentery, tuberculous enteritis, regional enteritis, lymphopathic venereum, and neoplasm. We have never seen chronic bacillary dysentery mimic ulcerative colitis; we have seen recurrences of ulcerative colitis induced by acute bacillary dysentery or similar intestinal infections. Amebic dysentery is usually differentiated by the history, the typical proctoscopic picture, and, above all, by the demonstration of the parasite. However, in occasional patients, after the amebae have been eradicated, the diarrhea persists and the proctoscopic picture is characteristic of ulcerative colitis. Tuberculous enteritis is recognized by the presence of the pulmonary lesion, the ileocecal location of the disease, and by the fact that the rectal involvement, if present,

* Read at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 31, 1949.

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The expenses incident to the bacteriologic studies were defrayed in part by a gift from Albert L. Hopkins; the psychiatric studies were in part subsidized by the income of courses in gastroenterology given under the auspices of the American College of Physicians in 1945 and 1946.

consists of the typical discrete ulcers. Regional enteritis is characterized by the classical clinical syndrome, the roentgenologic evidence, and the negative proctoscopic examination. There are some patients with ulcerative colitis, however, in whom the disease extends retrogradely from the cecum into the terminal ileum. Occasionally patients who have had ulcerative colitis for years will develop lesions of the small intestine with "skip areas" and the other classical features of regional enteritis. In lymphopathia venereum, one looks for the scar of the bubo and expects also a positive Frei reaction. The process is limited to the rectum and rectosigmoid; the strictures are concentric, thick, "fitting the finger snugly like a glove," whereas the strictures of ulcerative colitis are thin, eccentric, membranous, or fibrous. Neoplasm is usually differentiated easily by the history, rectal, proctoscopic, and roentgen-ray examinations. Bargen and Sauer [4] have shown that cancer develops in approximately 3 per cent of the patients with ulcerative colitis; the study of Cattell and Boehme [5] suggests that the incidence may be greater, perhaps 8 to 10 per cent.

Course

The course of the disease is characterized by apparently spontaneous remissions and exacerbations. Consequently, all evaluations of therapy are extremely difficult and of limited scientific validity. Furthermore, the course of the disease is so variable that it is scarcely possible to make comparisons from patient to patient, or indeed between groups of patients.[6, 7] In some individuals the process is merely a mild persistent or recurrent proctitis; in others it is a rather severe proctosigmoiditis; in others it is an acute febrile disease resembling typhoid fever, occasionally pursuing a fulminating course leading to death in a few weeks. The complications likewise are most protean.

Treatment

Treatment is primarily medical. It is handicapped by our ignorance of the basic cause of the disease, by the lack of a specific curative drug, and by the difficulty in evaluating therapeutic measures. This difficulty results from the spontaneously remitting nature of the malady and from the great, although often unrecognized, effect of psychotherapeutic forces. The following discussion of therapy is based upon certain physiologic principles, laboratory studies, and clinical observations.

Rest. Rest in bed is certainly indicated during the period of fever. Considerable difference of opinion exists as to how long it should be continued after the fever has subsided. There is some evidence that physical activity increases intestinal activity. Consequently, if the patient can be persuaded to remain in bed until the diarrhea, as well as the fever, has subsided, considerable benefit is often obtained. However, emotional turmoil also increases intestinal motility and hence it may be wise to permit the patient to be up and around before the diarrhea subsides. It is necessary to balance the physiologic benefit of rest against the psychotherapeutic value of

ambulation. We are convinced that with respect to rest, there is great similarity between the treatment of ulcerative colitis and pulmonary tuberculosis. It is well to recall the achievements of that physician extraordinary, the late Dr. Gerald B. Webb, his great skill in convincing people of the need for rest, and the devices he utilized for keeping them happy, his prescription of literature and scrapbooks.

Diet. The diet should be a high-caloric and high-protein, preferably of the low-residue, non-laxative type. Supplemental vitamins may be given as desired. Eating often constitutes a very great problem. Usually it is a mistake to dwell too much on the subject or to insist that patients eat. In some respects the situation is similar to that of the feeding problems of childhood. Food should be good, nutritious, well cooked, and tastefully served. Every effort should be made to tempt the patients to eat. As improvement occurs, the appetite returns and the intake of food increases. In periods of acute illness parenteral alimentation may be of great value. Tube feedings are occasionally helpful, but they must be handled with discretion. In some instances the program of medical (tube) ileostomy with formula feedings (by mouth or tube) as devised by Machella and Miller [9] are distinctly worth while. During such periods constant nursing and medical attention are essential.

Blood Transfusions. The rectal bleeding may be slight or exsanguinating. It is corrected best by large transfusions (500 to 600 c.c.) of whole blood given as often as necessary to maintain a normal blood picture. The prothrombin time under such conditions should always be checked, for it may be prolonged as a result of deficient absorption of vitamin K or hepatic disease. It may be advisable to administer vitamin K routinely by mouth or, in emergencies, parenterally.

Medication. Belladonna seems worth while although the antispasmodic drugs in general have only limited value.

Sedatives are helpful. Bromides are rarely given because of the danger of a rash or intoxication. Phenobarbital may be used to advantage over long periods of time; usually half a grain four times daily is sufficient, although agitated individuals should receive more. Other barbiturates may be given if insomnia persists. Occasionally chloral hydrate may be administered at night in doses ranging from 15 to 45 grains.

Opiates, in general, should be omitted because they increase the tonicity of the gut and are habit forming. Codeine may help a patient to sleep through the night, but the effect is usually transient. Occasionally either the tincture or the extract of opium may be used. The pain of ulcerative colitis is almost never sufficient to require the administration of morphine, demerol, or similar drugs.

With the advent of the chemotherapeutic drugs there was hope that a specific cure for ulcerative colitis would be found. On the whole, the early enthusiasm has given way to disappointment as each new antibiotic has failed to evoke a dramatic response. It was thought that by altering the

bacterial flora of the colon, information might be gained as to the rôle of various organisms. The ideal goal, of course, would be complete aerobic and anaerobic sterilization of the intestine. Thus far we have not been able to achieve this goal with any combination of drugs. Partial sterilization can be produced, but it is difficult to appraise the effect upon the disease. It may well be that at different times and in different individuals different bacteria are of pathogenic significance. It is known, for instance, that the peritonitis following perforation of the bowel is usually accompanied by a mixed bacterial flora. *B. coli*, considered to be non-pathogenic in the bowel, may be pathogenic in the peritoneum, urinary bladder, or blood stream. Various strains of *B. coli* behave differently, as do various strains of enterococci. Occasionally fecal cultures disclose the presence of pathogenic organisms, such as hemolytic streptococci or staphylococci, known to be susceptible to present day chemotherapy. Clinically it is difficult to escape the impression that these drugs are of some value; it is equally difficult to produce sufficient scientific evidence to give real substance to the impression. Nevertheless, it does seem to us worth while to determine the bacterial spectrum by fecal culture and to use the various chemotherapeutic agents.

The variations in the sulfonamides seem to be of minor importance. The soluble forms such as sulfadiazine have the advantage of permitting the drug to enter the blood stream as well as the lumen of the bowel. Perhaps for this reason, sulfaguanidine has seemed to be somewhat more satisfactory than sulfathalidine. It may be desirable to continue the administration of one of these drugs for several months. As a rule, the bacteriologic result is the conversion of the fecal flora from a predominantly gram negative one to gram positive.[10] There is some evidence that as the coliform organisms disappear, the enterococci increase.[11] In some patients, however, the coliform organisms are resistant to high concentrations of sulfonamide. Streptomycin given orally usually reduces or temporarily eradicates the coliform organisms.[12] Aureomycin, chloromycetin, and polymixin apparently alter the flora; our own experience is limited. Penicillin is primarily of value when pathogenic gram positive cocci are present.[13] While the ultimate value of chemotherapy in ulcerative colitis remains to be ascertained, our present impression is that it does constitute an important adjunct.

Psychotherapy. Numerous writers [14-18] have cited circumstantial if not experimental evidence of the rôle of emotional factors in this disease. Our observations are in accord. Emotional disturbances may precipitate exacerbations; whether they can initiate the process is less clear. As in so many diseases, it is difficult to distinguish between the psychosomatic and the somatopsychic reactions; a vicious circle is present with more or less complete regression of the personality to infantile levels. It is difficult to break the circle and bring about a maturing of the personality in the presence of such a truly miserable physical disease. We are convinced that the task is rarely one for the psychiatrist alone; we are likewise convinced of the enor-

mous value of intensive psychotherapy at the right time and under the proper circumstances.

In a sense the psychotherapy may be said to begin with skillful nursing care and control of the environment. These are essential, yet difficult to obtain. The family relationships are usually strained and for a variety of reasons: social, economic, and psychiatric. The physician must recognize the total situation and manage it as effectively as possible. The patient-physician relationship should be fostered deliberately and diligently. The patient needs an optimistic sympathetic friendly physician able to provide strong positive support continually together with intelligent reassurance. In the language of the psychiatrist, a strong positive transference is essential. The physician, however, must beware of too much counter transference because emotional involvement, either positive or negative in character, tends to warp the judgment and depreciate the therapy. As a rule, deep psychotherapy should not be undertaken by the physician. Furthermore, in the acute phases of the illness intense analytic therapy is best omitted, for the patient is then unable to deal with his conflicts and problems. Even in the remissions analytic therapy must be carried out cautiously because any emotional crisis such as that presented by an insoluble problem may precipitate a relapse. On the other hand, psychoanalysis carried out by an intelligent careful analyst may be of enormous value to the patient and lessen the burden of the physician in charge.

Surgery. The complications of ulcerative colitis often require surgical intervention although the disease itself is not benefited thereby. Some patients prefer ileostomy to prolonged medical treatment. There is no doubt that ileostomy with or without colectomy has restored many invalids to a life of useful and normal activity.[19, 20] The frequency with which the operation is indicated and will be indicated in the future for uncomplicated ulcerative colitis remains to be determined. There is some reason to think that modern chemotherapy and psychotherapy will greatly reduce the number of patients so treated. We do not think that our own past experience, or indeed that of anyone else, should be projected into the future. The recent report by Dennis [21] of good results following vagotomy is of interest. However, it seems to us to lack a rational basis. Diarrhea has been observed not infrequently after vagotomy for peptic ulcer. The only patient we have seen subjected to vagotomy for ulcerative colitis developed a recurrence within a year. Surgery is certainly indicated, however, for certain of the complications. Acute perforations may become walled off and recovery occur without laparotomy, but as a rule surgical repair is a safer procedure. Perianal abscesses and fistulae should be treated surgically as well as with the chemotherapeutic agents. Strictures of the colon may produce sufficient obstruction to require ileostomy usually followed by colectomy. Polyps present a challenging problem. Inflammatory hyperplasia leading to polyp formation is very common. As the inflammation subsides, the pseudopolyps may dis-

appear, but the polyps persist. The danger of carcinoma is very real. Colectomy is certainly indicated when neoplasm is detected, although it may indeed then be too late; prophylactic colectomy seems scarcely justifiable at the present time.

Illustrative Cases

It is not possible to discuss all of the details involved in the treatment of this disease or to present cases illustrating the numerous difficulties. Three patients have been chosen as typical of certain types; they illustrate some of the variations in the clinical picture and course as well as many of the therapeutic considerations.

Case 1. The patient, a young man, was perfectly well until June 1947 when at the age of 18 he was seized with a watery diarrhea while working as a dishwasher in a National Park restaurant. The diarrhea persisted through the summer. In September a physician performed a proctoscopic examination, examined rectal smears and feces, and made a diagnosis of amebic dysentery. Emetine and rest in bed were prescribed; the diarrhea ceased. Some time during the following winter or spring the diarrhea recurred. In June 1948 the patient's mother died of carcinoma of the rectum.

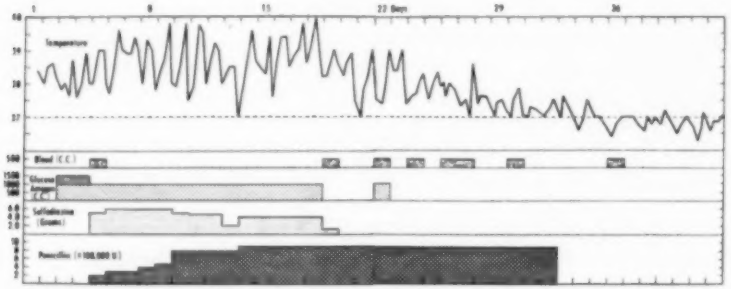

Fig. 1. Acute ulcerative colitis, clinical course of Case 1 with slow gradual recovery.

She had previously had ulcerative colitis for which an ileostomy and subtotal colectomy had been performed with spectacular success. The patient's diarrhea recurred during the fatal illness of his mother. He was admitted to the local hospital on September 28, 1948, and transferred to Billings Hospital on October 12, acutely ill with bloody diarrhea and fever, the course being shown in figure 1. Numerous fecal examinations for parasites and pathogenic organisms were negative.

Treatment consisted of rest in bed, parenteral alimentation, diet, chemotherapy with penicillin and sulfadiazine, blood transfusions, careful nursing, and supportive reassurance. The initial three weeks were stormy, the course resembling typhoid fever. In the fourth and fifth weeks the temperature subsided to normal. The patient gained steadily. The number of bowel movements decreased and their consistency improved. The appetite increased, and he gained weight rather rapidly. When discharged from the hospital on December 23, he was having only two or three stools per day instead of the 15 or more at the time of admission. Most of the stools were formed. Since his discharge the stools have all been formed and without gross blood. A proctoscopic examination on admission disclosed a thickened, polypoid,

friable, edematous mucosa covered with mucopurulent exudate; at present, the mucosa is slightly granular and not at all friable. The gain in weight has continued and the patient has now returned to school. He is continuing the diet and the belladonna, phenobarbital, and sulfaguanidine. The roentgenologic appearance of the colon in January 1949 is shown in figure 2.

Case 2. The patient, a girl 15 years of age, was perfectly well until May 1942, when she developed diarrhea following a week of nervous stress resulting from a high school initiation. Diarrhea persisted through the summer, complicated by thrombophlebitis of the right leg. She was hospitalized elsewhere. The diarrhea decreased temporarily but after her return home she continued to pass six to 10 loose or watery stools per day and lost 50 pounds in weight. The patient continued to be active and attend school in spite of the persistent diarrhea. In August 1945 she was treated with enemas of kerosene, following which there was a period of profuse bleeding.

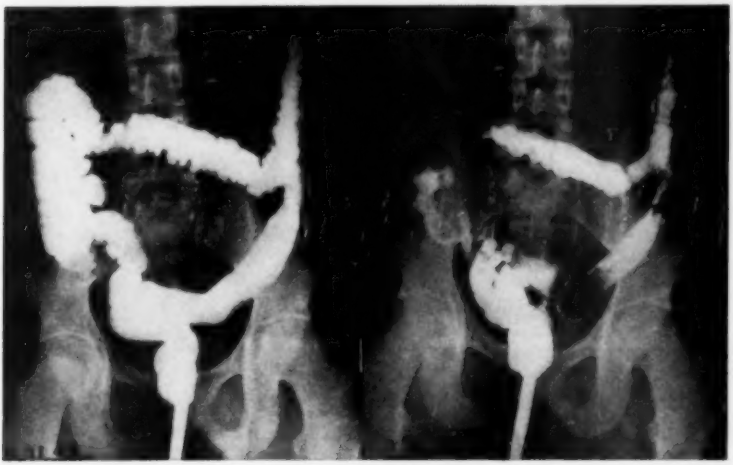

FIG. 2. Case 1. Roentgenologic appearance of the colon January 31, 1949, after recovery from the acute attack.

When admitted to the Billings Hospital on April 19, 1946, she was passing an average of six loose stools per day. Proctoscopic examination disclosed a diffusely granular, freely bleeding mucosa with a rigid lumen scarcely wide enough to permit the passage of the instrument. Examinations of rectal swabs and of the feces for parasites and pathogenic organisms were negative. Roentgenologic examination disclosed involvement of the entire colon, lack of haustral markings, and rigidity of the walls. The patient was hospitalized for 225 days, during which time there was very little fever. She received the usual diet and medication including sulfathalidine and three courses of penicillin. Her improvement was gradual and could not be specifically related to any particular medication or event. Seemingly endless hours were spent in the discussion of emotional problems.*

There was slow improvement, although at discharge on November 30, 1946, she was still having four to six soft bowel movements daily. The therapeutic program was continued at home, including almost complete bed rest. When she returned to

* Dr. Marion Dakin.

the clinic four months later, the stools had become formed and were reduced to two or three daily. Proctoscopic examination still disclosed an extremely friable mucosa with a moderate stricture in the region of the rectosigmoid. The program was continued through the summer of 1947. The stools were usually well formed. Proctoscopic examination revealed little edema and less friability of the wall. In January 1948 the rectum and mucosa appeared almost normal. In August 1948 the patient continued to have only one bowel movement per day, formed and of good caliber.

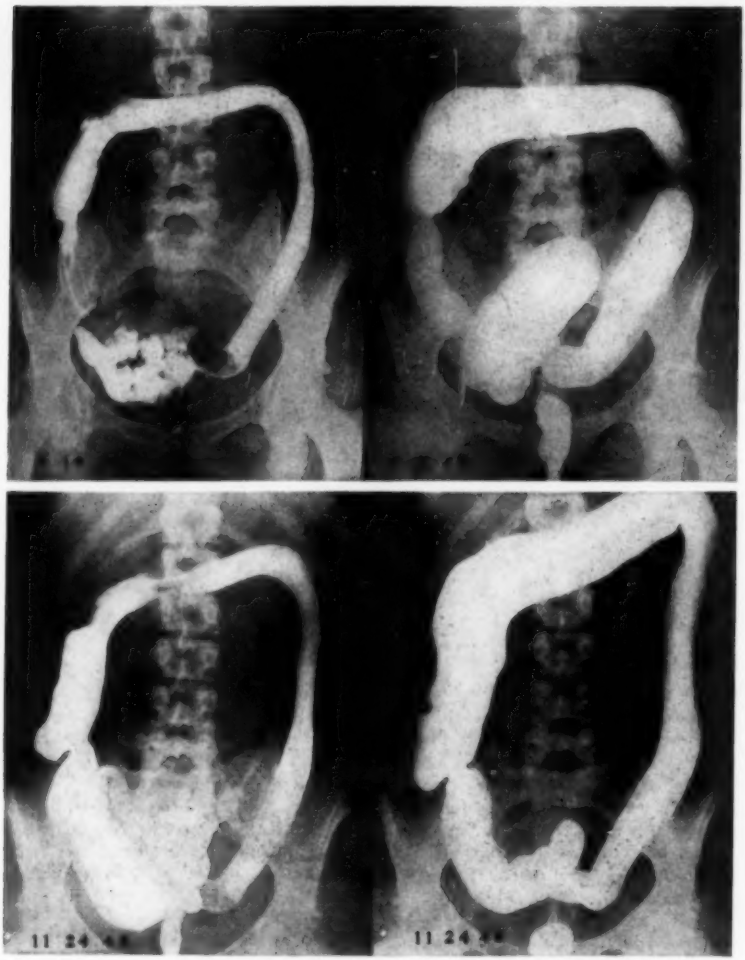

FIG. 3. Case 2. Roentgenologic appearance of the colon in April, 1946 (top) during the phase of chronic diarrhea, and in November, 1948 (bottom) after recovery with formed stools for 18 months. Note the shortening, rigidity of the walls and absence of haustral markings in all views.

Proctoscopic examination disclosed a scarred mucosa, not friable or edematous. The roentgen-ray examination in November 1948 again revealed involvement of the entire colon and of the ileum. The patient, now 22 years of age and in college, has been living a normal life since September 1947. There has been no recurrence of the diarrhea. She eats a general diet and takes no medication. Figure 3 shows the roentgenologic appearance of the colon in April 1946 and in November 1948. It is rather startling to realize that such extensive alteration of the structure of the colon exists in a patient who has been clinically well, rather obese, for two years, with no diarrhea, passing perfectly well formed defecations.

Case 3. A boy of 15 in 1941, experienced an attack of diarrhea of one week's duration. A similar episode nine months later lasted a few weeks and was followed by a third attack in nine months. An episode of diarrhea in the spring of 1944 lasted two months, subsided during the summer, and recurred in November, three weeks before his first admission to Billings Hospital on November 26. Proctoscopy revealed a friable, edematous mucosa. The patient was acutely ill, passing 10 to 20 blood-flecked stools daily. The course until the forty-ninth day was febrile in spite of sulfadiazine, sulfathalidine, and penicillin. However, gradual improvement did occur and the patient was discharged on February 12, 1945, after 79 days. Less than two

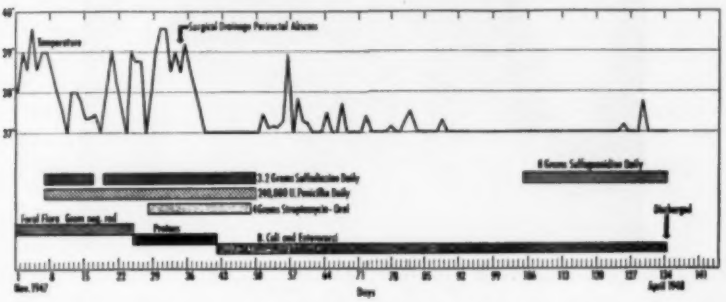

FIG. 4. Recurrent ulcerative colitis, clinical course of Case 3. Thirteenth (?) attack of diarrhea with febrile course subsiding following surgical drainage of a perirectal abscess. Complete recovery still present one year later.

months later the diarrhea gradually returned and the patient was readmitted to the hospital where he again ran a febrile course intermittently for 85 days. At the time of discharge on June 30, 1945, he was in fairly good condition. In October 1945 he was hospitalized elsewhere until December, gaining 20 pounds in weight. The stools decreased in number. In May 1946 he became worse again and was hospitalized for a few weeks in Chicago. Again in January 1947 he was hospitalized for three weeks because of acute arthritis and treated with artificial fever, sulfonamides, and penicillin.

In February 1947 he started school (pre-medical) and did well, gaining 15 pounds. In the late summer of 1947 emotional difficulties, which had been apparent all along, increased, and the patient entered upon a course of intensive psychoanalysis. He then began to pass more blood in the feces, lost weight, and developed fever. In September he was hospitalized because of severe hemorrhage from the bowel and shock. A hemorrhoidectomy was followed by a perirectal abscess and a fistula in ano. Another severe hemorrhage occurred and ileostomy was advised. On November 28, 1947, the patient was transferred to the Billings Hospital acutely ill. His course during the 133 days of subsequent hospitalization is shown graphically in figure 4.

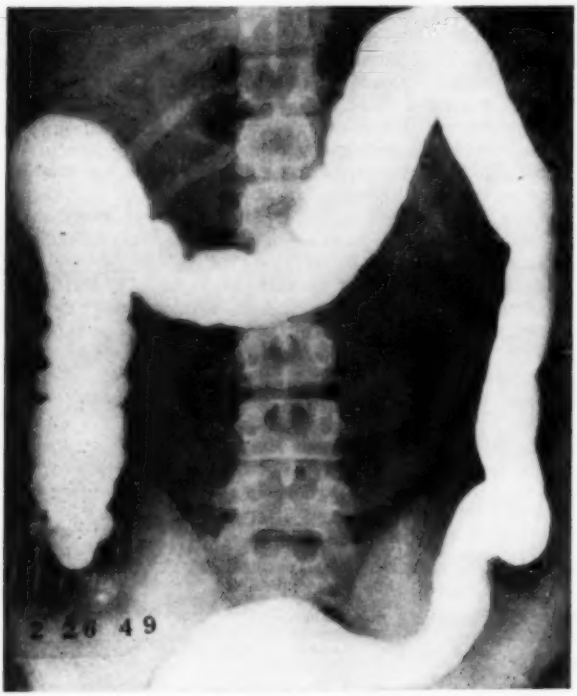

FIG. 5. Case 3. Roentgenologic appearance of colon after 13 (?) attacks of ulcerative colitis and complete recovery.

The fever subsided promptly after surgical drainage of a perirectal abscess and excision of the anal fistula. At the time of discharge, April 4, 1948, the stools were formed. The patient, now 23 years of age, has gained 66 pounds, weighing 180 pounds, passes one to three formed stools daily, has had no recurrence of the diarrhea, carries a full schedule of work, and seems in perfect health. Proctoscopy discloses a finely granular mucosa without edema or ulceration. Roentgenologically, the entire colon is seen to be shortened, smooth, and devoid of haustral markings (figure 5).

DISCUSSION

It is exceedingly difficult to appraise the rôle of the various therapeutic procedures in these three patients; perhaps they illustrate merely the natural course of the disease. We cannot escape the conclusion, however, that therapy did play a very vital rôle. In Case 1 the first emphasis was placed on good nursing care, parenteral alimentation, and transfusions of whole blood. Use of the Miller-Abbott tube (medical ileostomy) as suggested by Machella was seriously considered, but was not instituted because the patient was very apprehensive. In other similar patients the procedure has

been of value. As the patient gained confidence, he became more composed, began to eat, and slowly improved. The chemotherapy was administered empirically. There was no formal psychiatric inquiry or therapy. The disease apparently began as amebic dysentery and recurred as a non-specific type at about the time the patient's mother died of cancer of the rectum, developing on the basis of residual ulcerative colitis. The patient, an only child, was deeply attached to his mother. The transfer of the patient to the Billings Hospital 500 miles from his home brought him into the vicinity and supervision of an aunt who was a trained nurse and the wife of a physician. The aunt came from the same cultural background and served as a perfect substitute for the mother figure with real interest, warmth of affection and superb intelligence. Who can measure the contribution she made to the patient's recovery?

In Case 2, the extent of the recovery in terms of health and well being when contrasted with the extensively diseased colon is most dramatic. However, no incident in the process of recovery appeared dramatic at the time. One course of penicillin seemed to initiate improvement which was maintained when a placebo was substituted; a second course of penicillin given after the diarrhea had recurred had no effect. Formal psychiatric assistance was not available, but a physician * devoted innumerable hours to conferences with the patient and her family. The entire emotional constellation was extremely difficult. The patient, under the guidance of the physician,* accomplished an extensive reorganization of her attitudes. Many resentments, hostilities, and misunderstandings were overcome. This great improvement in the personality has persisted for two years during which time the patient has remained well.

Case 3 is in many respects the most difficult and most complicated of the three. The colon was not damaged as severely as in Case 2. On the other hand, the disease had extended over a period of seven years, requiring 10 separate hospitalizations for a total of 514 days in five different hospitals under many physicians. In general, the same measures were carried out in the various hospitals. In the last hospital admission the febrile course was not checked by sulfadiazine, penicillin, and streptomycin, nor did the rectal discharge become sterile. The temperature dropped suddenly after wide surgical drainage of a perirectal abscess and excision of the anal fistulae. Supportive therapy was used intensively. The patient had always been a bright, but insolent, disagreeable, and uncoöperative lad. Prior to his last hospitalization he had consulted a psychoanalyst,† who continued to see the patient regularly while he was hospitalized on the medical service. The details of the analytic sessions are not available and, in a sense, are unimportant; the significant and inescapable fact to us was the transformation in the personality of the patient as we watched him recover. While the question arises as to how much of this change is attributable to the analytic

* Dr. Marion Dakin.
† Dr. Henry H. Fineberg.

sessions, to the physical recovery, or to other factors, we are inclined to give great credit to the analyst.

The economic cost of ulcerative colitis is a heavy burden for most families. The expenditures made for the three patients described are not known. If one estimates the cost on the basis of the current ward rate of $10 per day, the amounts would be as follows:

Patient 1	85 days	$ 850
Patient 2	329 days	3290
Patient 3	514 days	5140

These figures do not include medications, special nurses, blood transfusions, and medical fees. Ileostomy with or without colectomy can be carried out in a shorter period of time at lower cost. From the financial point of view this may be the cheapest solution, but in our judgment it is not the most desirable one.

Summary

The treatment of ulcerative colitis is distinctly an individual problem because of the great variations in the extent of the disease, its severity, and in its spontaneous course as well as in the personalities of the individuals afflicted. An attempt has been made to sketch the varying rôles of rest, diet, medication, and nursing care together with the medical, surgical and psychiatric indications. Ulcerative colitis is considered an inflammatory process. Chemotherapy is important even though it is not possible at present to ascribe the disease to any specific organism or to produce complete sterilization of the intestine with the drugs available. Emotional factors are of great significance; they should be recognized and managed by the physician in charge or by a psychiatrist. Surgery is indicated primarily for the complications. Few diseases tax the resources of the patient and the physician to the extent that ulcerative colitis does; few are as costly; the rewards are life and health.

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STUDIES IN DISORDERS OF MUSCLE. II. CLINICAL MANIFESTATIONS AND INHERITANCE OF FACIOSCAPULOHUMERAL DYSTROPHY IN A LARGE FAMILY *

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Introduction

A study has been made of a large kindred † of which many members are known to have weakness and muscular atrophy. The individual family groups of this kindred are large and in some cases are of polygamous origin. This has presented an unusual opportunity for the study of the abnormality in a large group of patients, all of whom derived the trait from the same source; and to see the trait as it occurred at different ages and in different degrees of expression. A clinical description of the disease is presented as well as the pattern of its inheritance. Note is made also of associated hereditary characteristics and of other diseases found in this family.

Material and Methods

Twelve hundred and forty-nine individuals, descended from one dystrophic progenitor, make up the material from which our data were obtained. The kindred includes six generations known to have manifested the trait. Accurate information concerning the kindred has been derived from many sources including interviews with members of the family, church records and family records. As a result it has been possible to construct a well documented family pedigree (figures 1 and 2). A medical history and physical examination, as well as an intensive search for evidence of the trait, have been carried out by the authors in 240 individuals. Some of these examinations were performed in the Metabolic Ward of the Laboratory, others at clinics arranged at points conveniently located for the patients and the remainder in the homes of the respective families. Data concerning persons now deceased or not available for examination for other reasons were obtained from hospital records or from private physicians familiar with the trait. The late Dr. Samuel C. Baldwin spent many years studying the disease in this area and contributed valuable information about certain patients.

* Received for publication June 21, 1949.
From the Laboratory for the Study of Hereditary and Metabolic Disorders and the Departments of Medicine and Biology, University of Utah.
This study was supported in part by a grant from the United States Public Health Service.

† "Kindred" is used here in the genetic sense and refers to all persons descended from a single individual. "Family" is used in a more restricted sense and refers to a group of siblings and their parents.

A detailed search has been made for other traits which might be associated genetically with muscular dystrophy. This has included examination for the presence of associated anomalies and other disease processes, study of the various serological types of red blood cells and a search for other traits the inheritance of which is well established.

History of Kindred

Figures 1 and 2 are pedigree charts of the kindred. All members can be traced back to a common ancestor, I–1. He was born in England in 1775, migrated to Utah with the early pioneers, and died and was buried in Salt Lake City. Some of his children remained in England and others settled in the eastern United States. The rest of the family came to Utah. Whether or not the anomaly existed in the kindred prior to I–1 is not known. It is likely that it originated at some earlier time as a mutation. Members of the kindred can now be found in almost all parts of Utah and in many of the surrounding states.

Of the 1249 descendants of I–1, 159 are known to have had or to have the typical familial anomaly. This does not include all descendants of I–1 because information is not available concerning some family lines and because no attempt has been made to follow out certain lines known to be free of the trait. The pedigree charts in figures 1 and 2 include most but not all of those for whom we have good data. For example, certain individuals in each of the four generations descended from II–9 are known to be dystrophic. However, the information which we could obtain regarding other members of these families was inadequate and therefore the entire branch of the family has been excluded. Even when these were eliminated it was not practicable to include the entire group in one chart. The descendants of II–10 and of II–6 by his first wife are included in figure 1 and the descendants of II–6 by his second and third polygamous wives are included in figure 2.

Clinical Characteristics of the Disease

The disorder in this family presents a very characteristic clinical picture of facioscapulohumeral progressive muscular dystrophy. The following description of the disease is based on the detailed examinations of 58 members of this kindred who had the disorder.

The onset of symptoms or signs recognizable either by the patient or his family usually occurred between the ages of 7 and 20 years. The most common age of onset, as judged by symptoms, was 13 to 15 years. Table 1 shows the initial symptoms and the age at which they were first observed. It will be noted that there were a number of individuals who were unaware of the fact that they had inherited the disorder. One example is an elderly woman who reports that she first knew about her disability at the age of 55. Apparently it was pointed out to her then by a physician after the condition had become recognizable in her children. Several other older persons with

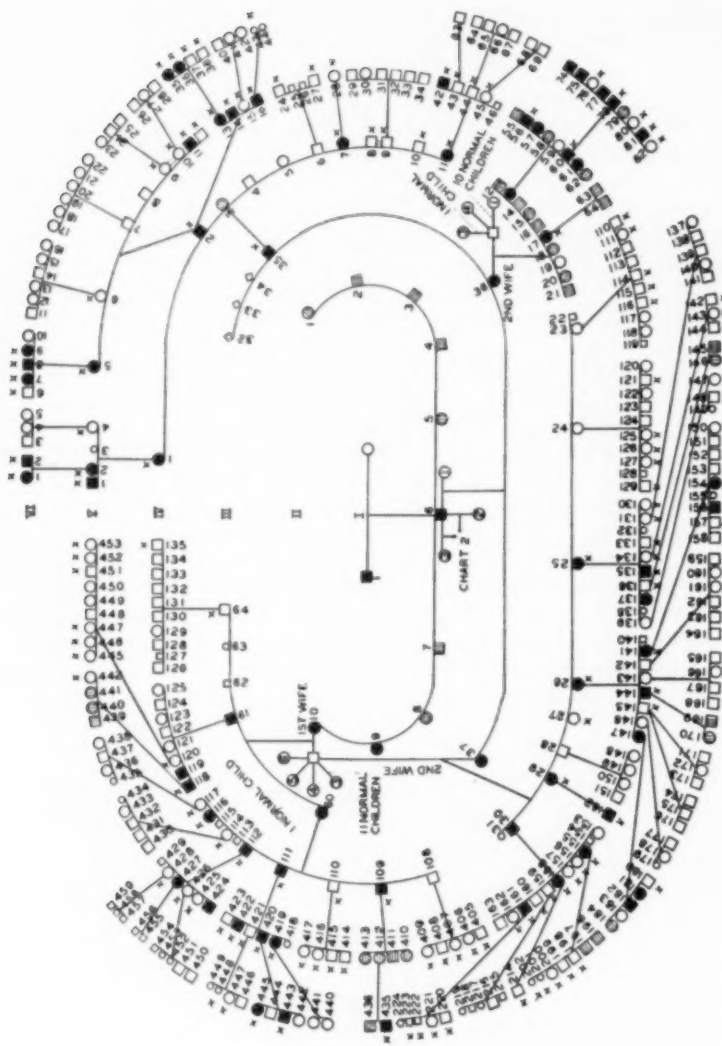


FIG. 1. Pedigree of kindred. The descendants of II-6 by his second and third wives are diagrammed separately in figure 2.

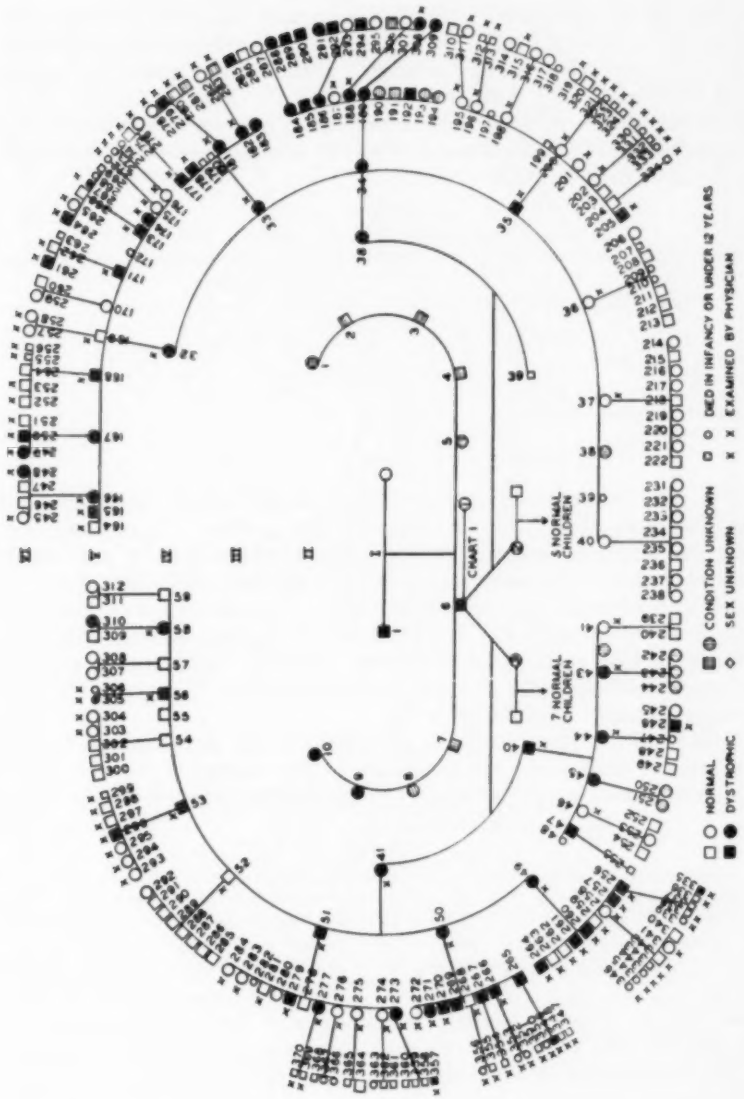


CHART I
5 NORMAL CHILDREN
7 NORMAL CHILDREN
NORMAL
DYSTROPHIC
CONDITION UNKNOWN
SEX UNKNOWN
DIED IN INFANCY OR UNDER 12 YEARS
EXAMINED BY PHYSICIAN

FIG. 2.

the disease did not recognize its nature at the time of onset and still have no significant disability but now can date it back to adolescence.

Although a large number of children have been seen, some of whom may be expected to develop the disease, characteristic manifestations could not be made out in any below the age of seven. Evaluation of muscle strength in young children is very difficult. Winging of the scapulae and anteriorly held shoulders were common in these children as they are in any large group of young children. In the absence of specific muscular weakness or atrophy the diagnosis was not made.

TABLE I

Age of Onset of Facioscapulohumeral Dystrophy in 58 Patients

Initial Symptom	Age at Onset						
	7–10	11–12	13	14	15	16–19	20 & over
Weakness in shoulders	1	1	7	4	7	8	4
Abnormal posture					1		1
No symptoms but findings on physical examination (age first examined)	5	1			1	4	13

The most common initial symptom was loss of the ability to raise the arms above the head or to hold them in that position. A smaller group first noted abnormal posture with or without recognizing its significance. The progression of weakness was very slow in all cases. No other symptoms related to the primary disorder were found. The correlation of age to severity is shown in table 2. The progressively higher incidence of serious involvement with each decade is evident. Equally significant, however, is the benign character of the disorder in many instances. Many aged patients were not seriously incapacitated.

The physical signs were those dependent on the weakness and atrophy of muscles. Table 3 shows the relation of the severity of the disorder to the muscles which were involved. The first muscles affected were the large

TABLE II

Correlation of Age to Severity in Facioscapulohumeral Dystrophy in 58 Patients

Degree of Involvement	Age at Examination							
	6–10	11–15	16–20	21–30	31–40	41–50	51–60	61 & over
Minimal—just detectable on examination	4	1	4		2	1	1	
Slight—evident but no significant disability		1	3	5	7	5	4	3
Moderate—some disability of arms and legs			1	1	1	4	3	3
Severe—unable to stand without support					1		1	2

muscles of the pectoral girdle and the muscles of the face. Atrophy and weakness of all of the facial muscles were usually present. The zygomaticus was most severely involved. The abnormality was most characteristic in the muscles about the mouth and resulted from the slightly asymmetrical atrophy of the orbicularis oris. Inability to pucker the lips and to whistle in this fashion was very striking. No real loss of voluntary ability to control the movements of the lips was present, the awkward movements being the result, apparently, of the patchy asymmetric atrophy. Figure 3 illustrates the abnormality in a patient with severe involvement of the face.

TABLE III

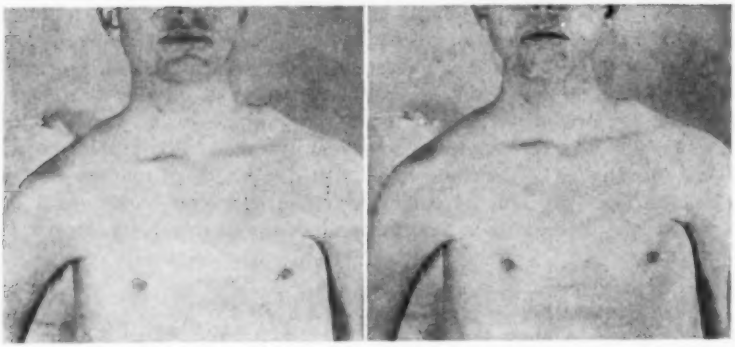
Pattern of Muscular Involvement in Facioscapulohumeral Dystrophy in 58 Patients

Muscle	Degree of Involvement of Certain Muscles in Typical Cases at Different Stages			
	Minimal	Slight	Moderate	Severe
Facial except orbicularis oris and zygomaticus	0	0	1	2
Orbicularis oris	1	2	3	3
Zygomaticus	2	3	4	4
Sternomastoid, sternal head	0	1	2	3
Pectoralis major, sternal head	1	2	4	4
Pectoralis major, clavicular head	0	1	2	2
Deltoid	0	1	2	3
Triceps and biceps	0	0	2	3
Brachioradialis	1	2	4	4
Trapezius, upper fibers	0	0	1	2
Trapezius, middle and lower fibers	2	2–3	3–4	4
Rhomboids	0	0	3	4
Latissimi	1	3	4	4
Abdominals and recti abdominus	0	0	2	3
Glutei	0	1	2	3
Thigh groups	0	1	2	3
Tibials	1	2	3	4
Peroneals	0	0	2	3
Calf group	0	0	1	2
Hands, forearms, feet, etc.	0	0	1	2

0. No change
1. Atrophy with significant weakness
2. Moderate atrophy and weakness
3. Severe disability
4. No muscle detectable

These facial changes produce rather grotesque, and apparently incoördinate, movements of the lips which are extremely characteristic and practically diagnostic when present. In spite of these changes, phonation is usually well within the range of normal.

Involvement of the neck muscles was usually moderate. The sternomastoid muscles were moderately reduced in size but were almost never absent, in contrast to their early and severe involvement in myotonia dystrophica. The clavicular head frequently was less atrophic than the sternal head.



a b

FIG. 3. The left hand picture shows the face at rest in a 29 year old man with rather severe involvement of facial muscles. On the right the result of his attempt to whistle by pursing his lips is demonstrated. Some degree of this anomaly in the facial muscles about the mouth is present in nearly every case. The extreme muscular atrophy of the pectoral girdle muscles is evident.

FIG. 4. Patient with moderately severe muscle atrophy. Note that the axillary folds slope toward the clavicular-manubrial junction as the result of the atrophy of the sternal head of the pectoralis major. Also contrast the good forearm musculature (except brachioradialis) and the atrophic pectoral girdle and upper arm musculature. The loss in the upper deltoid in contrast to its lower segment is evident.

Atrophy in the pectoralis major was striking and began very early. It was much more severe in the sternal head than in the clavicular head, with the result that the axillary folds sloped toward the claviculo-manubrial joints instead of toward the xiphoid process (figure 4). The trapezius was remarkable because of the very early complete loss of its lower fibers and fair preservation of the upper fibers (figures 5 and 6). The localized atrophy within the pectoralis major and trapezius was the earliest and most reliable sign of the disorder. The loss of the lower and middle fibers of the trapezius in association with more or less complete loss of the latissimi dorsi, resulted in elevation of the scapulae, a striking feature in roentgen-ray films of the chest (figures 6 and 7).

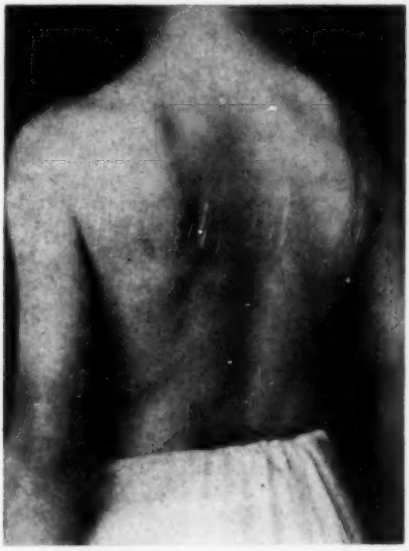


FIG. 5. Minimal involvement with good muscle mass and strength except in the lower and middle fibers of the trapezius which are atrophic, allowing the contours of the rhomboids to show through.

The rhomboids were frequently completely lost. Atrophy in the supra- and infra-scapularis was moderate and progressive. Severe atrophy also occurred in the deeper muscles of the pectoral girdle but this was of less diagnostic value because of the greater difficulty in evaluating the amount of loss.

Rather striking flattening of the entire anterior chest was observed in almost all of the moderately advanced and severe cases. This was the result of the loss of the anterior cervical and pectoral girdle musculature, of the anterior position of the shoulders, and of actual flattening of the anterior rib cage. More severe deformity with extreme depression of the lower end

a b

FIG. 6. Severe involvement of pectoral girdle muscles. The important features are: nearly complete absence of muscles attached to the scapula except for fibers of the upper trapezius; the high, diagonal and anterior position of the scapula; flattening of anterior chest with atrophy of anterior pectoral girdle muscles and prominence of the clavicles.

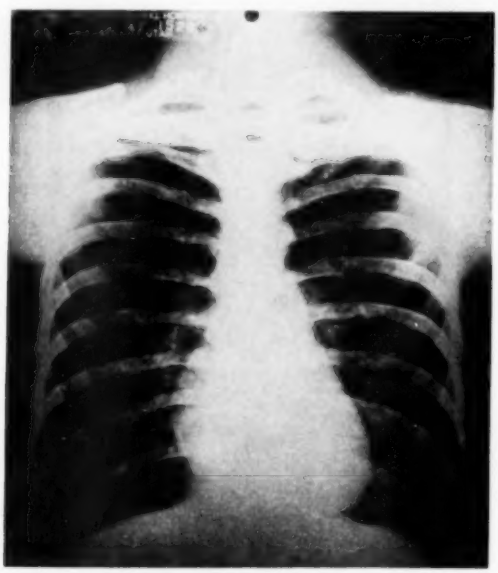
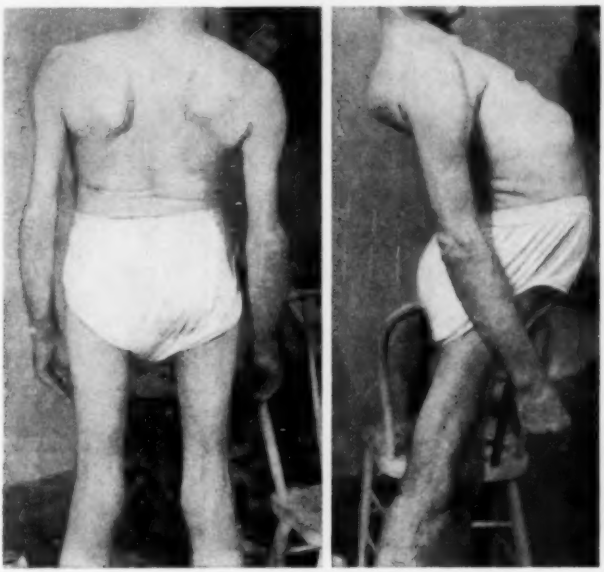


FIG. 7. A postero-anterior film of the chest which shows the abnormal position of the scapulae in a patient with only slight disability resulting from his disease.

of the sternum and xiphoid (*pectus excavatum*) was present in most of the severely disabled patients. The *pectus excavatum* seemed to be more or less proportional in its severity to the degree of muscle loss and probably was caused primarily by loss of the sternal head of the pectoralis major and of the serratus anterior. This interpretation may be incorrect, however, since one individual (V–169) was observed who had minimal pectus excavatum not unlike that seen in his dystrophic relatives but without any evident weakness or atrophy of pectoral muscles. Another comparable deformity of the sternum in an otherwise normal individual (IV–114) is said to have been the result of trauma to the chest.



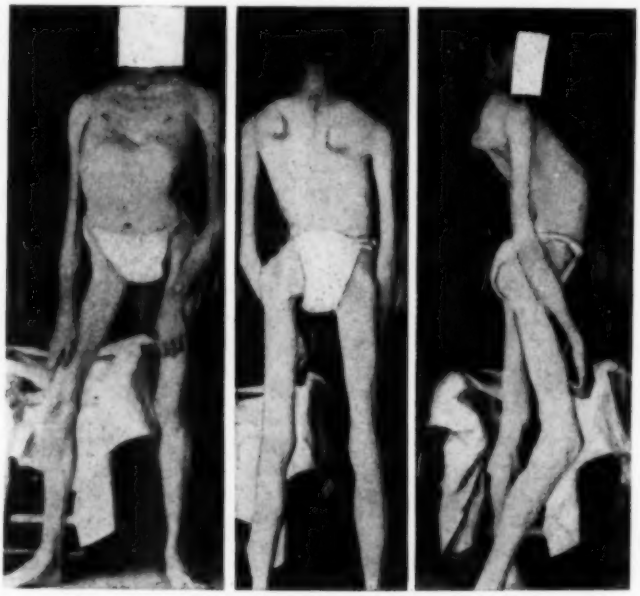
a b

FIG. 8. Characteristic lordosis in a patient with moderately severe disease. Note that the pelvis is more anterior than in other common types of lordosis with the result that the line of weight bearing from shoulders to feet passes posteriorly to the sacrum.

The deltoid usually showed its most severe loss in the proximal portion, a major part of the muscle tissue sometimes remaining at its insertion (figure 4). The combined loss of scapular muscles and the deltoids resulted in loss of ability to elevate and abduct the upper arm. The biceps and triceps brachii were frequently atrophic. The forearm and hand muscle remained intact or nearly so until the late stages of the disease except for the brachioradialis which was lost very early. Bilateral loss of the brachioradialis is another early and reliable sign of the presence of dystrophy. Thus

supination is frequently rather weak in advanced forms of the disease but pronation is usually of normal strength.

Atrophy of the erector spinae musculature was a moderately late development and was associated with loss of the deep muscles of the pelvis. These changes resulted in a striking lordosis (figures 7 and 9) with a waddling, rather grotesque, gait not seen often in other diseases except in other dystrophies. Such atrophy is even more characteristic of the childhood type and is responsible in both disorders for the maneuver of erecting the trunk by pushing against the legs (Gower's sign).

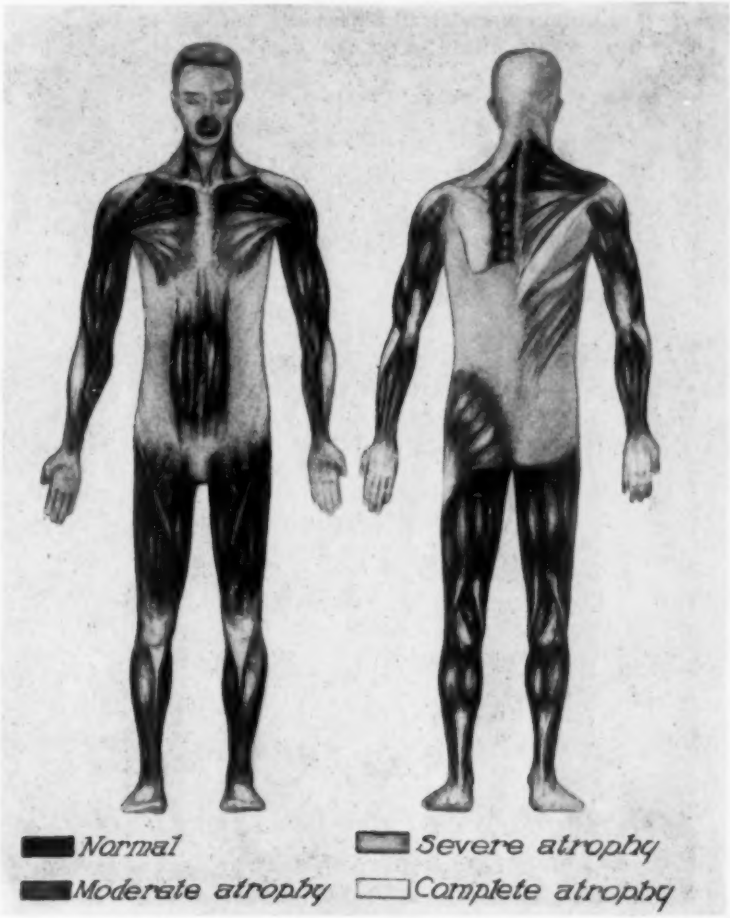


a b c

FIG. 9. Severe disability in a young adult. Note the advanced character of the muscular atrophy, but maintenance of the pattern of muscles involved.

Involvement of the thigh muscles was present frequently but was of functional significance only in individuals with severe muscular atrophy elsewhere (figure 9). In the earlier stages of the disorder much more severe involvement was present in the pectoral girdle muscles than in any other group. The loss of peroneal and tibial muscles began early in the course of the disorder and foot drop was occasionally an early symptom. Preservation of the calf muscles was the rule with good strength remaining in plantar flexion and in the intrinsic muscles of the feet. Striking preservation of the calf muscles in contrast to the other muscles of the lower leg sometimes

produced the appearance of the so-called "pseudohypertrophy" seen in many individuals with the childhood type of dystrophy. Only one patient, however, had calf muscles with the firm, inelastic texture of the muscular enlargement of the childhood type. Whether or not this represents the same process in both diseases is not clear. Figure 10 illustrates the extent and



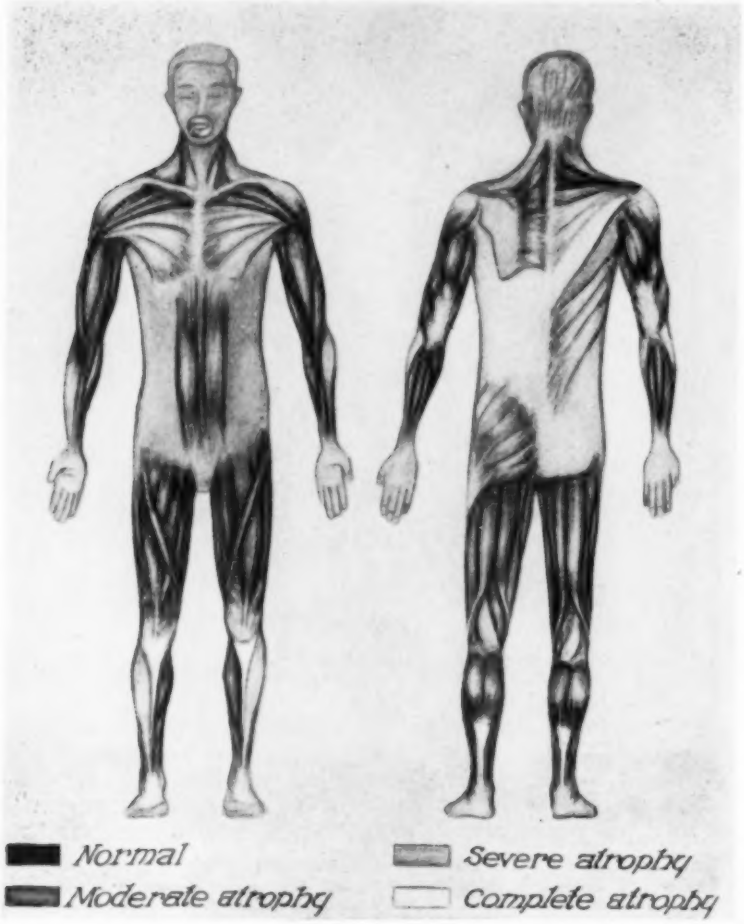
a. Slight

FIG. 10. (a, slight; b, moderate (page 652); c, severe (page 653)). Schematic drawing of the pattern of muscular atrophy at three stages of the progression of facioscapulohumeral progressive muscular dystrophy. Only those easily examined muscles which are of diagnostic aid have been included. In the views of the back the trapezius has been represented on the left and the rhomboids on the right.

degree of involvement of the easily examined muscles in various stages of facioscapulohumeral dystrophy.

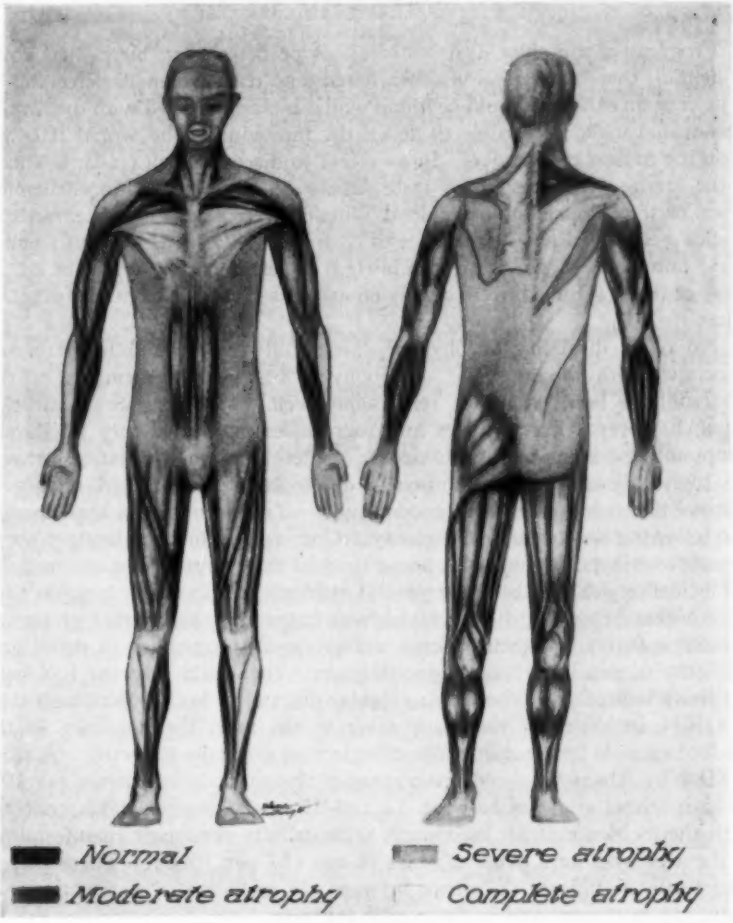
The rate of progression of the muscular atrophy was quite variable in different individuals, as tables 2 and 3 emphasize. Intercurrent illnesses had little effect on the rate of progression but immobilization for long periods particularly by body casts resulted in rapid progression of the muscular atrophy. The pattern of muscular involvement was not changed, however.

The great majority of these people have lived, or are enjoying, a normal



b. Moderate

FIG. 10. See page 651 for legend.



c. Severe

FIG. 10. See page 651 for legend.

life span with only minor disabilities. Certain others have more seriously incapacitating disabilities, and a few, particularly those of advanced age, are bed or wheel chair invalids (table 3). One young man of 29 years showed extremely severe muscular loss which had been complicated by two auto accidents and ensuing immobilization because of fractures (figure 9). In spite of this, with occasional aid in getting from car to chair, he continued an active life as an accountant. He also had rheumatic heart disease and has since died with symptoms suggesting congestive heart failure.

Associated Traits and Diseases

Progressive muscular dystrophy cannot be detected at birth. It would be helpful, therefore, if some other hereditary trait which is detectable at birth or at an early age could be found which is closely linked with dystrophy. This would make it possible to detect the individuals who would later develop the muscular disorder. In an effort to discover such traits, members of the kindred were tested for taste deficiency, using phenylthiocarbamide. From each person examined, blood samples were taken and the red corpuscles were tested for the presence of A, B, M, N, D (Rh°) C (rh′) and E (rh″) antigens. From these data fairly complete genotypes could be set up. None of these, if linked, were closely enough associated to be of any practical value.

No other disability or physical abnormality was found to be closely associated with the muscular dystrophy. Most of the members of this kindred have been otherwise remarkably well. Two exceptions must be noted, however. Five females and four males gave a history or showed symptoms and signs of thyrotoxicosis. There was no correlation between the thyrotoxicosis and the muscular dystrophy. Several had undergone subtotal thyroidectomies with good results. Two women had hypothyroidism following subtotal thyroidectomy. One woman had moderately severe spontaneous hypothyroidism. Some thyroid enlargement was common but the incidence was not above the general incidence in this endemic goiter area.

Another important disease which was frequently seen in this group was rheumatic fever. Sixteen patients among the 240 examined in detail gave a history of manifestations suggesting acute rheumatic fever or had heart murmurs indicative of rheumatic valvular disease, or both. Although there is a high incidence of rheumatic fever in the area, the incidence in this kindred exceeds by a considerable margin that normally expected. A study in Utah by Alway [1] showed seven cases of rheumatic heart disease per 1000 in high school students between 14 and 16 years of age. This contrasts with the incidence of 16 individuals with definite rheumatic manifestations in the 184 who were over 12 years of age (87 per 1000). There was no statistically significant difference between the incidence of rheumatic manifestations in normal and in dystrophic subjects.

Of special interest to us was the search for other muscular and neurological disorders among the members of this kindred.

One elderly woman (IV–120) developed a progressively incapacitating disease in her fifties which was typical of the combined system disease frequently found in association with pernicious anemia. She had none of the other clinical or laboratory findings of pernicious anemia, however, even gastric secretion being normal. She was considered to have "lateral sclerosis." She also had mild hypothyroidism but there was no muscle atrophy of the type found in other members in whom the dystrophy trait was present. All of her children are free of evidence of dystrophy.

No cases suggestive of the childhood type of dystrophy or of myotonia or other hereditary neurological or muscular disorders were found. In one adult (V–19) without dystrophy a classical scalenus anticus syndrome was encountered. The history that two sisters of another sibship were involved in a local epidemic of Western equine encephalitis with subsequent mental deficiency and convulsions was obtained. It has not been possible to see the sister who is still living. One patient (V–157) had a tremor characteristic of extrapyramidal motor disease. She gave no history of encephalitis and did not have peripheral arteriosclerosis. One member (V–66) of the kindred had suffered a recent severe attack of acute anterior poliomyelitis with residual paralysis.

The systolic and diastolic blood pressures were elevated in six patients. Three showed definite manifestations of arteriosclerotic heart disease, two with typical histories of acute myocardial infarction. Two non-dystrophic patients had epilepsy. A number of other diseases were found in isolated individuals.

Nature of Inheritance

In analyzing the data concerning the transmission of the trait for facioscapulohumeral dystrophy only those families for which accurate information regarding nearly all of the members was available, were used in our calculations. Families with many children below the age of 12 years were also eliminated because identification of the trait is difficult in children.

The families used for analysis in which one parent, either male or female, was dystrophic, are shown in table 4. Of a total of 273 children in these families, 130 are affected with dystrophy and 143 are normal. Table 5 compares the observed with the expected results on a 1 : 1 basis. It will be seen that the deviations are not significant, being only 0.79 times the standard error.

Reference to figures 1 and 2 shows that no relationship to order of birth is present. This conforms with the random occurrence expected in the inheritance of a genetic character. Of equal importance is the absence of affected individuals among the children of persons who are known not to manifest the trait and, conversely, the absence of any breaks in the line of involved individuals through the six generations. All of this demonstrates the complete penetrance of the character. This is also confirmed by the 1 : 1 ratio which is expected in similar crosses involving traits transmitted as simple Mendelian dominants with complete penetrance. In this kindred dystrophic members have married only normal individuals and therefore the matings are simple back crosses of heterozygous dominants to homozygous normal individuals.

It is quite evident that the inheritance is that of a dominant trait. The trait has been transmitted by the dystrophic parent to approximately one-half of his offspring and has never been transmitted by a non-dystrophic parent.

TABLE IV

Parent	Children						Died in Infancy	
	Dystrophy		Normal		Condition unknown			
	Male	Female	Male	Female	Male	Female	Male	Female
II–6	1	2					3	
II–6		1					1	
II–6	1	1						
II–10	1	1	1				1	1
III–35	1	3	5	1		1		
III–37	1	3	1	3			1	1
III–38	1	3		3		1		1
III–40	1	3		2		1		1
III–41	3	3	5					
III–60	3	1	2	2			2	
III–61	2		2	4				
IV–1	1	1		1				1
IV–2	1	1	3	3				
IV–2	2	1		1				
IV–7				1				
IV–11	1		2	1			1	
IV–13	2	2		1	1	2		
IV–25	1	1	2	4				2
IV–26	1	2	2	2			1	
IV–29	1							
IV–30	1	2	3	4			1	
IV–32	4	3	2	3				1
IV–33	2	3					2	
IV–34	2	4		1	1	3		
IV–35	1		2	6			1	1
IV–44	1		2	1				1
IV–49	5		3	1				
IV–50	5	1	1	1				
IV–51	1	2	2	6				1
IV–53	1		3	3				
IV–56		1		1				
IV–58		1	1					
IV–111	2	1	2					1
IV–112	1	1		3			1	
V–2	1	1						
V–5	1	2	1	1				
V–13		2	2					
V–60	5			3		1		
V–141	1	1	5	1				1
V–147	1	1	1	1		1		
V–155			2	1	2			2
V–158			1					
V–161			1	1			2	1
V–166		1	2	1				
V–167	1	1	1					
V–171	1		1				1	
V–177			1	1				
V–182				1	1			
V–184	3	1	1	1				
V–186	2	1		2				
V–188		1		1	1			
V–189		1						
V–419				2				
V–420	1	1	1	1				
Total	68	62	66	77	6	10	15	16
	130		143					

Further evidence of dominance is shown in the polygamous matings. II–6 had three wives. Two of these had been married previously and had had children by their first husbands. These children and their descendants have shown no muscular dystrophy. Six of the 10 children in the three families by the dystrophic husband had dystrophy. Again, the husband of II–10 and III–36 both of whom were dystrophic, had several other wives who were not dystrophic and by whom he had families. None of the children of these non-dystrophic marriages showed dystrophy while at least two of the children of each of the two dystrophic wives were affected.

Because the known matings in the kindred represent back crosses (Ddxdd), we have no way of knowing whether dominance is complete or incomplete. That is, the homozygous condition has not been observed. It would be necessary to know the clinical manifestations in such a person before one could determine the completeness of dominance.

Only two consanguineous marriages are known to have occurred in this kindred. IV–132 married his second cousin V–20. Neither was dystrophic. They had three normal children. IV–133, who was non-dystrophic married his third cousin, V–182, who was dystrophic.

TABLE V

Phenotypes	Observed	Calculated	Deviation	S.E.r	Dev. S.E.r
Normal (dd)	143	136.5	6.5	8.26	.79
Dystrophic (Dd)	130	136.5	6.5		
Totals	273	273.0			

As has been pointed out above, the penetrance is complete. The expressivity varies greatly and has been described in the section on clinical manifestations. Since there is such a wide range of expression from very slight to very severe, one might expect to find a rare individual who would have the defect in such a slight degree that it could not be detected by physical examination and yet this individual could transmit the abnormal gene to his or her children. Out of the many cases examined, however, no such person has been discovered.

The ratio of normal to abnormal children even in moderate sized families deviated widely from the average. In table 4 it may be seen that IV–34 had six dystrophic and only one normal child among the seven examined in spite of the fact that the manifestations of the disorder in her at the age of 56 were so minimal that its nature had not been recognized and it caused her inconvenience only in such activities as combing her hair. On the other hand, IV–53 had six normal and only one dystrophic child in spite of the fact that he, a man 65 years of age, had been a wheel chair invalid for years.

Discussion

Landouzy and Déjerine [2] first described facioscapulohumeral progressive muscular dystrophy in 1885. They found nine cases in four generations of one kindred. No cases were found in the second generation. Eulenberg and Cohn,[3] Weitz,[4] Niwa [5] and Minkowski and Sidler [6] recognized the occurrence of facioscapulohumeral dystrophy in a pattern of inheritance consistent with a dominant gene but their data were relatively small in any particular family.

Robinson [7] studied 20 family groups of one kindred extending over five generations. He described the trait in this kindred as differing in certain respects from other types of dystrophy previously described and enumerated the distinguishing characteristics. Of 128 children one of whose parents was affected with "familial myopathy" (as he named it), 82 were affected and 46 were normal. This is nearer a 2:1 than the 1:1 ratio which would be expected for the dominant inheritance which he suggests. On the basis of extensive information which we have obtained on this same kindred [8] we believe that many of the distinguishing characteristics which he described as well as the above ratio were inaccurate. The trait is facioscapulohumeral dystrophy and the inheritance is typically dominant just as in that described for the kindred which is the subject of this report. Many other studies of the inheritance of dystrophy have been made but their significance is made uncertain by failure to distinguish between the types of dystrophy. Certain of the most important of these have been discussed in a previous report.[9]

Certain principles important in the study of human genetics have been emphasized by our experience with this kindred. Members of the family are frequently unreliable sources of information concerning the others in the family who manifest the trait. This is particularly true in disorders such as progressive muscular dystrophy in which a wide variability in the expression of the trait occurs. Minimally affected cases are missed. On the other hand, anyone who has any type of neuromuscular disorder is apt to be considered as manifesting the trait. For example, the patients described above with lateral sclerosis and the scalenus anticus syndrome had been considered to be dystrophic for many years, but neither they nor their children show evidence of muscular dystrophy. Again, minor manifestations can be identified easily when familiarity is gained with the trait although they may not be evident even to a well trained neurologist who is not familiar with the variability of the disease.

It is clear from the data on this kindred that the severity of the disorder in the parent had little influence on the severity of the condition in the children. Some of the most severe cases have been observed in the offspring of parents showing only a slight degree of dystrophy; on the other hand, some of the children of certain of the most severely affected individuals have shown only minor signs. No evidence that "anticipation" or "antedating" in the sense that has been suggested as occurring in association with certain

other inheritable characters occurs in this disorder. Although certain individual families may suggest this, the occurrence of the reverse shows that simple variation in expression of the trait explains the findings adequately. The fact that patients with severe manifestations and others with mild symptoms have had large families permits one to be certain about this and may explain the occurrence of apparent "anticipation" in certain other diseases where severe involvement precludes large families, e.g., diabetes mellitus and myotonia dystrophica.

In diabetes mellitus and in myotonia dystrophica it has been observed frequently that in the children of those with disease of mild or moderate severity the condition appeared earlier or more severely than in their parents. This has led most authors to conclude that the disease process becomes more and more severe as it passes from generation to generation. An equally tenable explanation, however, is that variability in the expression of the disorder is the significant factor and that the reverse type of variation is prevented by the nature of the diseases which preclude procreation in very severe cases.

It would seem that a dominant gene for dystrophy is transmitted but that the severity of its expression depends upon the environment and the remaining genotype of the individual concerned. Where symptoms of dystrophy begin at an early age, the disease progresses more rapidly. Just what factors are responsible for this early appearance of symptoms is not known, nor is it understood why the disease progresses more rapidly in younger individuals than in persons first showing signs at a later age.

On the basis of the type of study reported here, reliable information can be given to both involved and uninvolved members of the family concerning the risk which they take of passing the trait to their children. For example, in this kindred, adults with no sign of the disorder take no significant risk while those with signs, regardless of their magnitude, are apt to have children with the disorder in unpredictable severity. Such prospective parents can then determine for themselves the desirability of having children.

Summary

1. A study of 1249 individuals in a single kindred in which facioscapulohumeral dystrophy occurred is presented.

2. Fifty-eight members of the kindred who manifest the trait were studied. The clinical manifestations of facioscapulohumeral dystrophy as it occurs in this family consist chiefly in a characteristic pattern and progression of atrophy of facial, pectoral girdle and other muscles. The disease is usually benign, only an occasional patient being severely handicapped.

3. A typical Mendelian dominant pattern of inheritance with complete penetrance and variable expressivity has been demonstrated.

4. The occurrence of other diseases and traits has been studied in detail but no significant correlation with progressive muscular dystrophy has been found.

We are indebted to a number of physicians who have aided with examinations of patients who could not be examined by us. Mrs. M. S. Parker has been of invaluable assistance in field work. We are also indebted to the members of the family who have been coöperative and helpful in nearly all instances.

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AUREOMYCIN IN URINARY TRACT INFECTIONS—PRELIMINARY CLINICAL REPORT*

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Urinary tract infection is second only to upper respiratory infection in incidence. Moreover, the causative organisms are easily identified. The treatment of such infections, however, often taxes the ability of the ablest clinician.

Of the many pathogenic bacteria that have at one time or another been isolated from the urine, only about a half dozen cause us repeated and frequent concern. Urinary organisms are immediately separated into gram negative bacilli or gram positive cocci. Among the gram negative bacilli we invariably find, either singly or in combination,

1. *Escherichia coli*
2. *Aerobacter aerogenes*
3. *Pseudomonas aeruginosa* (*B. pyocyaneus*)
4. *Proteus vulgaris*

The important gram positive cocci are:

1. *Streptococcus fecalis* (Enterococcus)
2. *Staphylococcus*

When mixed infections occur it is the gram negative organisms which are important and challenge our therapeutic skill. Chemotherapy and the antibiotics have achieved great success in controlling some of these important organisms, especially penicillin in gram positive coccal infections and streptomycin for the gram negative bacilli. These organisms, however, were not to be easily controlled, and soon penicillin resistant and streptomycin resistant microörganisms developed.

In 1948, Duggar of the Lederle Laboratories of the American Cyanamid Company reported a new antibiotic which he named aureomycin. This remarkable new mold extract has many important features which suggest it may supplant penicillin and streptomycin in urologic infections. It is a drug which combines minimal toxic manifestations with an indifference to the ingenuity of bacteria; for with rare exceptions, no significant aureomycin resistance develops. Moreover it is active in vitro against many penicillin resistant and streptomycin resistant microörganisms.

Finland and his co-workers found it difficult to cultivate organisms which became resistant to aureomycin. Of six strains repeatedly subcultured, they

* Received for publication June 21, 1949.
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found only one strain of *Aerobacter aerogenes* increased in resistance; its resistance increased 32-fold during 30 transfers with, however, no further increase during 40 additional transfers. These investigators also found (*a*) that the size of the inoculum influences the concentration of aureomycin required to inhibit the growth of bacteria, (*b*) that aureomycin is effective only against vigorously multiplying organisms, and (*c*) that aureomycin is much more effective in an acid than in an alkaline medium.

The microörganisms which are inhibited by aureomycin are legion and include many gram positive cocci, including the streptococcus, staphylococcus and enterococcus, which are of importance in urinary tract infections; and also most of the gram negative bacilli which are affected by streptomycin, including *Aerobacter aerogenes* and *B. coli,* but unfortunately not including *Pseudomonas aeruginosa* and *Proteus vulgaris.* These organisms remain the bugbear of the urologist, though their threat is steadily decreasing, for streptomycin is effective against pyocyaneus, and polymixin, though nephrotoxic, is effectual against *B. proteus.* Aureomycin is also active against many of the larger virus infections such as lymphogranuloma venereum and primary atypical pneumonias, against rickettsial infections, and also against spirochetes as noted in Weil's disease and syphilis. Success has also been reported in non-specific urethritis, but this application has been unsuccessful in our experience.

Aureomycin is a dry golden yellow powder and under the trade name of Duomycin is available as a stable preparation in 250 mg. capsules. Intravenous therapy is not at present available although it soon will be through the use of a sodium salt. Intramuscular injections of a 1 per cent concentration in distilled water or glucose cause pain, but this can be reduced by the addition of novocaine. Parenteral therapy is not advantageous, however, as oral therapy is fully effectual. Aureomycin is readily absorbed. Blood level determinations are difficult because of the deterioration of the drug in alkaline media, and because of the neutralizing effect of the serum proteins. Dowling, however, reported that with doses of 300 mg. of aureomycin peak levels in the serum of 5 micrograms were evident after three hours, and the drug was still detectable in the serum at the end of 12 hours. Dosages of 700 mg. achieved a peak of 9 micrograms at six hours, and the drug was still detectable at 12 hours.

Aureomycin appears rapidly in the urine and fairly high concentrations can be obtained. Its excretion is continuous. It is present in the urine in the one hour specimen, reaching a peak concentration between four to eight hours. Activity of aureomycin in the urine is detectable up to two to three days, when between 12 and 15 per cent of the oral dosage can be recovered in the urine. Concentrations up to 256 micrograms per cubic centimeter have been found. The urinary concentration, however, varies with the oral dosage and usually a delay of six to 12 hours has been noted before urinary excretion in an adequate concentration has been observed. With an initial oral dose of 30 milligrams per kilogram per day (500 mg.

four times a day), the urinary concentration reached 80 to 160 micrograms per milliliter. When the oral dosage was 15 milligrams per kilogram per day (250 mg. four times a day), the urine level varied from 20 to 80 micrograms per milliliter (Schoenbach). Oral doses of 0.5 to 0.75 gm. daily reached a concentration of 64 to 256 micrograms per milliliter in urine collected two to 16 hours later (Finland). The optimum period between oral doses in order to maintain optimum urinary concentration is about six hours.

With the above facts of absorption and excretion in mind we can profitably review the reaction of the organisms to optimum concentrations of aureomycin (table 1). Chandler and Bliss found that *Staphylococcus* and *Streptococcus fecalis* were inhibited by less than one microgram of aureomycin per c.c. of media, *B. coli* and *aerogenes* by 2.5 to 5 micrograms aureomycin, and that the resistant organisms *Pseudomonas aeruginosa* and *Proteus vulgaris* were not inhibited by 20 micrograms of aureomycin. Finland found that these two stubborn offenders were inhibited at concentrations between 125 to 250 micrograms, while the susceptible organisms succumbed at concentrations of 1 to 25 micrograms per milliliter of media.

TABLE I

Composite Table on Organism Sensitivity to Concentrations of Aureomycin

Concentration Necessary to Inhibit in 24 Hours (Price)		Concentration for No Viability (Price)	Micrograms Aureomycin Inhibitory (Chandler and Bliss)	Micrograms per Milliliter Aureomycin for Inhibition (Finland)
B. coli	1.56–3.12	25–200	2.5 to 5 micrograms per cubic centimeter	1–25
Aerobacter aerogenes	X	X	2.5 to 5 micrograms per cubic centimeter	1–25
Pseudomonas aeruginosa	50	—	More than 20 micrograms per cubic centimeter	125–250
Proteus vulgaris	3.12	50	More than 20 micrograms per cubic centimeter	125–250
Staphylococcus	.09–25	50	Less than 1 microgram per cubic centimeter	1.25
Enterococcus	50	50–200	Less than 1 microgram per cubic centimeter	1.25

The optimal oral dosage of aureomycin is still to be worked out. As much as 4 to 6 gm. daily for two weeks were given by Spink et al. to prevent relapse in brucellosis without untoward effects.

We have used two dosage schedules in the cases here reported and we have varied the duration of dosage considerably since. To our office patients we give 500 mg. oral aureomycin four times a day for the first day (approximately 30 milligrams per kilogram average size adult) and 250 mg. four times a day for the next two days (approximately 15 milligrams per kilogram).

In our hospitalized patients we have given a five day course of therapy beginning with 250 mg. aureomycin every hour for six doses, then every two hours for the next nine doses, then every four hours for 12 doses and finally every six hours for eight more doses. This latter schedule represents an initial dose of 3.75 grams the first day, 1.5 grams the next two days and 1 gram on the fourth and fifth days.

The dosage schedule followed by Collins et al. in treating their cases of urinary tract infections lasted for seven days in doses of 500 mg. morning and evening. Those patients receiving a second course, usually after an interval of two weeks, received 500 mg. four times a day. Schoenbach et al. in their case used a daily dose of 600 mg. divided into six doses and continued therapy for 11 days. This was a case of coli-aerogenes infection which exhibited inhibition by 5.0 micrograms per milliliter in vitro. At the end of treatment, the concentration of aureomycin in the urine was 80 micrograms per milliliter, but a heavy growth of secondarily infecting *B. proteus* was present. Their second patient was given aureomycin for seven days. Here, too, the coli-aerogenes pyelonephritis cleared up and a *B. proteus* infection supervened.

One of the remarkable things about aureomycin is its disinclination to cause any toxicity. Thorough reviews of their cases by Finland, by Schoenbach and by others have failed to reveal any toxicity or idiosyncratic type of response such as rash, drug fever, etc. Looseness of the stool, however, was a very frequent finding. Normal bowel action was again evident after discontinuance of the drug. Next in frequency was the occurrence of nausea, occasionally with vomiting. Only rarely is it necessary to discontinue the use of the drug because of the vomiting; Amphojel helps in these cases. In one case of severe nausea and vomiting in a patient with frequent severe migraine headaches, the drug was discontinued for 12 hours and then readministered with return of only mild nausea without vomiting. Dizziness and malaise have also been complained of, as well as dryness of the mouth in two cases.

A complication, which has heretofore never been reported, has been observed in a number of our patients—microscopic hematuria with red blood cells in the centrifuged urine, varying from five to loaded red blood cells per high power field. One case had a frank and rather severe hematuria with the passage of two large clots. Investigations by Schoenbach et al. of the blood picture and blood chemistries have failed to reveal any abnormal response in their cases. Animal experiments by Harned et al. revealed no toxic effects on the kidneys. In dogs following four doses only traces of albumin appeared temporarily in the urine. The only positive effect of aureomycin on the kidneys is its mild diuretic action. When urea is assigned the value of one (assayed by the Lipschitz rat method), Duomycin has an activity of 12.6 and can be compared as to diuretic actions with caffeine, 32 and theobromine, 115.

Case Reports

Case 1. A woman, age 40, had a stone removed from the right ureter three years ago. She had a 13 year history of a stone in the right kidney and had had repeated episodes of chills and fever which did not respond to sulfonamides or penicillin. Urine, microscopically, was loaded with pus cells and bacteria. A culture revealed *B. coli* and *Aerobacter aerogenes.* Aureomycin was given. Toxicity in the form of mild diarrhea and dizziness occurred. The following day the urine became clear and microscopically revealed only an occasional white blood cell. Patient maintained marked clinical improvement.

Case 2. A patient 42 years of age had a 10 year history of bilateral renal calculous hydronephrosis with repeated episodes of backache, chills and fever. There had also been numerous attacks of acute pyelonephritis. Repeated therapy with sulfonamides, penicillin and streptomycin had given temporary relief. The urine was thick and milky and microscopically was loaded with pus cells and pus clumps. Culture revealed *B. coli* and *Aerobacter aerogenes.* Aureomycin was given and immediately thereafter the urine became clearer and revealed only 75 pus cells with an occasional red blood cell per high power field. A second course of aureomycin was given and the urine became clearer and microscopically revealed five to seven pus cells per high power field. Clinical improvement was marked, but complete and persistently clear urine could not be obtained.

Case 3. This patient 56 years of age had had the right kidney removed because of calculi at age 25. On admission there were multiple calculi in the lower pole of her solitary kidney. Patient complained only of an occasional left backache but passed cloudy urine which microscopically revealed from 20 to innumerable pus cells per high power field with occasional red blood cells. Urine culture revealed *B. coli.* Aureomycin was given and toxicity in the form of dizziness, nausea and vomiting followed; however, the urine became clear on the second day of treatment and microscopically showed only two or three pus cells per high power field. One week after aureomycin was discontinued, the urine again became cloudy and aureomycin was again given with the same satisfactory result. Clinical improvement was very evident.

Case 4. A patient, age 67, had had a bladder resection for malignant papilloma and a prostatectomy in 1943. He returned because of poor erections. Examination of the urine revealed 10 to 15 pus cells per high power field and many bacteria. Sulfonamides were temporarily effectual in clearing the urine. Later, penicillin was tried and finally ammonium mandelate without benefit. Microscopic examination of the urine still revealed 5 to 10 pus cells with marked bacilluria. Culture revealed *B. coli* and *Staphylococcus aureus.* Aureomycin was prescribed and the following day the urine was clear and microscopically revealed only occasional pus cell without organisms or red blood cells. No toxic symptoms were present. Clinical cure obtained.

Case 5. A patient, age 37, had had his left kidney removed elsewhere. An infected ureteral stump had been left in situ and five years after the operation on the kidney a left lower quadrant abscess opened through the abdominal wall. The patient also presented bladder symptoms and infected urine. Repeated courses of sulfonamides, penicillin and streptomycin did not relieve his malaise and frequency. The urine was cloudy and microscopically showed many pus cells and was loaded with organisms. Culture revealed *Aerobacter aerogenes.* Aureomycin was prescribed and the following day the urine cleared, malaise disappeared, appetite returned and patient felt "good." Microscopic examination of urine revealed five pus cells per high power field. Patient felt well for eight days and then again had anorexia, malaise, fever to 101° F. and cloudy urine. Microscopically there were many pus

cells and streptobacilli, on methylene blue stain. A second course of aureomycin again left him feeling very well with clear urine. This time he had some nausea and mild diarrhea with aureomycin. After 10 days he had relapse and a third course of aureomycin was prescribed. On the second day of this course, he had marked nausea and repeated vomiting. The next day his temperature rose to 103° and, in addition, the patient experienced frank hematuria. The following day he passed two large blood clots, and thereafter the urine started to clear. Cystoscopy was performed and a slightly edematous and infected bladder mucosa was the only positive finding. The urine later became cloudy with 7 to 10 pus cells to the high power field but the patient continued to feel better clinically.

Case 6. A patient, age 33, had had a calculus removed from his left kidney in 1948. A recurrent stone was in evidence on his return. Voided specimen of urine was cloudy and microscopically revealed many pus cells, pus clumps and bacteria. Sulfonamides and penicillin were ineffectual. The urine culture grew *B. coli*, and aureomycin was given. The urine became clear and microscopically showed no pus cells, but two or three red blood cells were present. After 10 days the urine again became cloudy and a second course of aureomycin was given. At this time patient had looseness of the bowels; however, he felt well and the urine again cleared, showing only two or three pus cells to a high power field. Clinical improvement was very evident.

Case 7. A man, age 61, had had suprapubic prostatectomy two months previously and the urine was still cloudy. Urine culture showed *B. coli*. Microscopically the urine was loaded with pus cells. The patient was given penicillin without benefit and, because he was sensitive to sulfonamide, aureomycin was then given. No toxic symptoms were noted. The urine became clearer and microscopically showed three to five pus cells but also six red blood cells per high power field. Some clinical improvement was noted.

Case 8. A patient, age 55, had recurrent left renal calculus. The urine was cloudy and microscopically showed many pus cells with a few red blood cells. Urine culture revealed *Pseudomonas aeruginosa*. A course of aureomycin was given. This caused some dizziness and diarrhea. The urine did not clear up though the number of pus cells was less (50 pus cells and 7 to 10 red blood cells to high power field). No clinical improvement was noted.

Case 9. A patient, age 61, had had a long standing history of cystitis and trigonitis with marked bacilluria. Repeated courses with various sulfonamides were given without benefit. Urine culture revealed *B. coli*. A course of aureomycin was given. No toxic symptoms were present except for lower abdominal discomfort. The urine became clear on the second day and has remained clear. Marked clinical improvement.

Case 10. A patient, age 58, had bilateral renal calculi removed in 1942 and 1943 and returned for routine examination, which revealed many pus cells and pus clumps. A course of a sulfonamide had no effect. Urine culture was reported *Pseudomonas aeruginosa*. Treatment with aureomycin was accompanied by a slight increase in the number of stools, otherwise patient felt well. The urine became microscopically negative. Clinical cure.

Case 11. A patient, age 51, had been treated for repeated attacks of left pyelonephritis. The urine persistently revealed about 25 pus cells and two or three red blood cells per high power field. Because of the persistent backache, a course of aureomycin was given after a urine culture of *Staphylococcus aureus* was obtained. Aureomycin produced slight nausea, no vomiting and slight diarrhea. The urine, however, became clear and microscopically showed only occasional pus cells. Two weeks later the urine was still clear with three to five pus cells per high power field. Clinical improvement was noteworthy.

Case 12. This patient, age 49, had bilateral calculous pyohydronephrosis and stones had been removed from each side in July 1948 and January 1949. Patient returned in chronic azotemia. The urine was cloudy and microscopically showed many pus cells. Courses of sulfonamides and penicillin were ineffectual and streptomycin, which had originally been effective, had become ineffectual. Culture of the urine revealed *B. pyocyaneus* and *Aerobacter aerogenes.* Aureomycin was prescribed. It caused dizziness and edema of eyelids with some nausea but no vomiting. The urine, however, became clear and the patient showed clinical improvement.

Case 13. A patient, age 67, had had calculi removed from the left kidney in 1944 and 1945 and had also had a pyeloplasty for avulsion of the ureter from the pelvis. Subsequently the patient passed several calculi from the left kidney. On return she complained of left backache, and showed many pus cells in the urine. Sulfonamides were ineffectual; repeated penicillin courses were partly effectual but finally had to be discontinued because of dizziness. Ammonium mandelate and pyridium were also without effect. Culture revealed *Aerobacter aerogenes* and proteus. A course of aureomycin was given without toxic manifestation; but no clinical improvement occurred. Microscopically, the urine continued to show 10 to 20 pus cells and many red blood cells per high power field.

Case 14. A patient, age 73, had had a suprapubic prostatectomy in 1948, and since has had cloudy urine which microscopically showed 20 to 30 pus cells per high power field. Sulfonamides were ineffectual. Culture revealed *B. proteus.* Aureomycin was administered. The only toxic manifestation was frequent morning stools. Clinically no improvement was noted and microscopically the urine still showed 15 pus cells per high power field and also now five to six red blood cells per high power field.

Case 15. This patient, age 41, had bilateral polycystic disease with chronic azotemia and chronic pyelonephritis, bilateral. Sulfonamides were occasionally of some benefit and so was penicillin. The patient retained right lumbar pain; the catheterized specimen of urine continued to show many pus cells. Urine culture revealed *Aerobacter aerogenes.* A course of aureomycin was accompanied by considerable exhaustion, dizziness and nausea. Clinical improvement was marked but temporary.

Case 16. A patient, age 60, had a history of bladder symptoms due to interstitial cystitis. The urine microscopically showed many pus cells and bacilli, and urine culture revealed *Staphylococcus aureus.* A course of aureomycin was prescribed. The only toxic symptom was dryness of the mouth. The urine appeared clear but microscopically showed 10 to 15 pus cells and also 30 red blood cells per high power field. The bladder symptoms subsided considerably. Frequency, formerly every hour, diminished after aureomycin therapy to every three hours. Considerable general improvement was manifested.

Case 17. This patient, age 44, had had transvesical diverticulectomies and transurethral resections of the bladder neck; the last resection was in July 1948. Since resection, the urine had been very cloudy and infected. Repeated courses of sulfonamides, penicillin and streptomycin, with argyrol and permanganate of potash locally, had all been ineffectual.

The urine was found milky and loaded with pus cells; the urine culture revealed *Aerobacter aerogenes.* Aureomycin was prescribed; examination of urine on successive days revealed progressively fewer pus cells though the urine never cleared. A second course of aureomycin was given which produced considerable nausea and vomiting. Aureomycin was discontinued with the fourteenth capsule. The urine cleared and microscopically revealed only one or two pus cells but now many red blood cells were present. The patient also complained of bladder discomfort. Upon

cystoscopic examination the bladder mucosa was found injected throughout. A small adherent clot 2 mm. in diameter was removed. The urine thereafter remained clear of pus cells and red blood cells. Clinical cure was evident.

Case 18. A patient, age 58, gave a five year history of dysuria, worse during the last six months with considerable tenesmus, burning on urination and urgency. Left backache was prominent. A diagnosis of left pyelonephritis, cystitis and trigonitis was made. The urine showed one or two pus cells per high power field and was loaded with organisms. The urine culture grew *Streptococcus fecalis.* She was placed on aureomycin. There were no toxic manifestations. Immediately thereafter, patient felt much better, the urine became clear, and microscopically negative. Relief of her dysuria and frequency occurred. Clinical cure obtained.

Case 19. A 45 year old patient had polycystic renal disease and had had a Goldstein procedure performed on each side. Her urine thereafter remained cloudy and microscopically revealed many pus cells and bacilli. Courses of sulfonamides and penicillin were ineffectual. Culture of the urine revealed *B. proteus.* Nevertheless, a course of aureomycin was prescribed. No change in the microscopic examination of urine was observed. No clinical change.

Case 20. A patient 46 years of age had had the left kidney removed for calculous pyohydronephrosis in 1947. Because of a resistant cystitis the urine had never cleared since his discharge from the hospital, despite repeated courses of sulfonamides and penicillin. Temporary improvement followed streptomycin, and was noted also following local irrigation with potassium permanganate. Recent urine examination revealed four or five pus cells microscopically with many bacilli present. Culture revealed *Aerobacter aerogenes.* A course of aureomycin was given. No toxic effects of aureomycin occurred. The urine cleared and microscopically became negative. The patient felt well. Clinical cure obtained.

Case 21. A 50 year old patient gave a history of bilateral renal calculi with left hydronephrosis. She was admitted in azotemia with pyelonephritis, chills and fever, and anemia. Urine culture revealed *B. pyocyaneus.* Following an attack of chills and fever the patient was given penicillin without response. She was resistant and sensitive to streptomycin. Aureomycin was prescribed. The temperature dropped by crisis. The urine cleared, though cultures continued to reveal the presence of pyocyaneus and proteus. Since then, she has had a left pyelolithotomy performed and she has improved considerably.

Case 22. A patient, age 65, gave a history of chills and fever with lower back pain. Cystoscopy revealed the presence of a left renal tumor. Following cystoscopy the patient developed a *B. coli* septicemia which did not respond to streptomycin or penicillin. Aureomycin was given and followed by a dramatic response. The temperature dropped by crisis. Urine culture thereafter revealed only yeast cells.

Case 23. A 53 year old patient was admitted with left renal calculi which were removed. The urine culture during convalescence grew *Aerobacter aerogenes.* A course of aureomycin was given which resulted in clear urine and normal temperature. Culture thereafter revealed *B. proteus.* However, the patient felt well. The wound healed rapidly and the urine became clear. No cellular elements were present microscopically. Clinical cure obtained.

Case 24. A patient 36 years of age who had been paraplegic since 1942 was admitted to Sinai Hospital in 1948, with overflow incontinence. Resection of the vesical neck was performed and following this procedure, patient had a very stormy course with repeated chills and fever up to 106° F. Repeated cultures revealed the presence of mixed infection in spite of repeated courses of chemotherapy and antibiotics in the form of penicillin and streptomycin. The patient was again admitted because of chills and fever, severe anemia and azotemia resulting from his urinary

infection. A suprapubic cystostomy was performed. The clinical condition improved but the urine remained infected. Culture revealed *B. coli* and *Aerobacter aerogenes* and he was then started on a course of aureomycin. Immediately thereafter the temperature became normal and the urine clear. However, culture still revealed the presence of *B. proteus*.

Case 25. A patient 38 years of age had multiple and bilateral renal calculi. The right kidney had been removed in 1941 for calculous pyohydronephrosis. Since then, he had had pain in the left side from his renal calculi and also chills and fever from the infected urine. Urine culture revealed pyocyaneus. A course of aureomycin was given. His urine became clearer but still contained many pus cells, and a culture after therapy revealed pyocyaneus and proteus.

TABLE II

Summary of Cases

Case	Sex	Age	Diagnosis	Culture	Dose*	Urine		Results			Toxicity
						Pre	Post	Excellent	Good	Poor	
1	F	40	R. cal. pyelo.	Coli Aerob.	16	3+ pc org.	occ. pc		X		Dizziness Diarrhea
2	M	42	Bil. cal. pyoneph.	Coli Aerob.	32	3+ pc	(a) 2+ pc occ. rbc (b) occ. pc		XT†		
3	F	56	L. cal. pyoneph.	*B. coli*	16	3+ pc occ. rbc	occ. pc		XT†		Dizziness Nausea Vomiting
4	M	67	Cystitis	Coli *Staph. aur.*	16	1+ pc org.	occ. pc	X			
5	M	37	Cystitis	Aerob.	48	3+ pc org.	(a) occ. pc (b) occ. pc (c) occ. pc		XT†		Nausea Diarrhea †T. hemat.
6	M	33	Bil. pyelo. L. cal. pyo.	Coli	16	3+ pc org.	no pc 2–3 rbc		X		Diarrhea
7	M	61	Cystitis	Coli	16	3+ pc	2+ pc 6 rbc			X	
8	M	55	L. cal. pyelo.	Pyocyan.	16	3+ pc few rbc	1+ pc 7–10 rbc			X	Dizziness Diarrhea
9	F	61	Cystitis	*B. coli*	16	Bacill.	no pc	X			Lower abd. discomfort
10	M	58	Chr. pyelo.	Pyocyan.	16	3+ pc	no pc	X			Diarrhea
11	M	51	L. pyelo.	*Staph. aur.*	16	1+ pc occ. rbc	occ. pc	X			Nausea Diarrhea
12	F	49	Bil. cal. Pyoneph.	Pyocyan. Aerob.	16	3+ pc	no pc		X		Dizziness Blurred vision
13	F	67	L. pyelo.	Aerob. Proteus	16	3+ pc	2+ pc many rbc			X	
14	M	73	Cystitis	Proteus	16	3+ pc	2+ pc 5–6 rbc			X	Diarrhea
15	F	41	Bil. polycy. Chr. pyelo.	Aerob.	16	3+ pc	no pc		XT†		Exhaustion Dizziness Nausea

* 250 mg. capsules (16 capsules to a course).
† T—Temporary.

TABLE II—*Continued*

Case	Sex	Age	Diagnosis	Culture	Dose*	Urine		Results			Toxicity
						Pre	Post	Excellent	Good	Poor	
16	F	60	Inter. cystitis	*Staph. aur.*	16	3+ pc org.	occ. pc 30 rbc		X		Dry mouth
17	M	44	Cystitis	Aerob.	48	3+ pc	(a) no pc (b) occ. pc 3+ rbc	X			Nausea Vomiting Bl. discomf.
18	F	58	L. pyelo. cystitis	*Strep. fecalis*	16	occ. pc org.	no pc	X			
19	F	45	Polycystic pyelo.	*B. proteus*	16	3+ pc org.	3+ pc org.			X	
20	M	46	R. pyelo. cystitis	Aerob.	16	occ. pc bacill.	no pc	X			
21	F	50	Bil. pyelo. L. cal.	Pyocyan.	26	Cloudy 3+ pc	Pyocyan. Proteus		XT†		
22	F	65	Kidney tumor septicemia	*B. coli*	26		Yeast	X			
23	M	53	L. ureterit.	Aerob.	16	Cloudy 3+ pc	no pc	X			
24	M	36	Paraplegia pyelo. cystitis	Coli Aerob.	26	Cloudy 3+ pc	no pc *B. prot.*		XT†		
25	M	38	L. cal. pyohydroneph.	Pyocyan.	16	Very cloudy 3+ pc	Cloudy Pyocyan. Proteus		XT†		

* 250 mg. capsules (16 capsules to a course).
† T—Temporary.

RESULTS

The results obtained with the use of aureomycin even in our small series are felt to be noteworthy. This group of 25 patients has only been a "scout" series to determine for us a dosage schedule, the length of time medication should be persisted in, the type of organisms affected, and the type of urologic disease best controlled by aureomycin.

This has not been an easy series for aureomycin because we chose for therapy not recent infections, but our most stubborn cases, infections that have been long standing and which have clinically defied many and varied therapeutic approaches.

The urologic diseases (of infective nature) treated with aureomycin are varied and include recurrent acute and chronic pyelonephritis, infected hydronephrosis and calculous pyohydronephrosis, urolithiasis, chronic ureteritis and both recurrent acute and chronic cystitis. In addition to some of the obstructive uropathies, many of these patients have had repeated instrumentations, two have had recent prostatectomies and one a recent ureterolithotomy.

The results as noted were indeed gratifying. Only five cases were outright failures. Of these, two were proteus infections and one *B. coli*. It has been repeatedly observed that aureomycin is ineffectual against urinary infections due to proteus and pyocyaneus. Our cases substantiate this view.

although one case had a pure culture of pyocyaneus and clinical cure was obtained. Three patients had satisfactory results but only of a temporary nature. The failure of the case of *B. coli* cystitis (Case 7) to clear might be explained as due to too short a course of aureomycin therapy. Our other cases of *B. coli* infections gave us satisfactory to excellent results.

Good results of a permanent nature were obtained in nine cases and of a temporary nature in 11 more. We firmly believe, however, that more cures could have been obtained if the course of aureomycin therapy had been extended over a week or 10 days.

Aureomycin has a bacteriostatic effect rather than a bactericidal effect as shown by Chandler and Bliss, and in order for one to accomplish a bactericidal effect, the dosage would have to be increased beyond clinical application. Because of these facts, many of our good results were of a temporary nature (nine out of 12), with grossly clear urine which became cloudy again after a week or two. One must therefore be cautious about accepting a cure when the urine becomes clear or microscopically free of pus cells, because frequently a gram stain of the centrifuged specimen or a culture will reveal the organisms to be still present. Undoubtedly, a longer course of therapy could keep the urine clear and also perhaps permit the natural body forces to overcome the infection and achieve permanent eradication of the infective process.

Another very important point is brought out in this preliminary short series of cases—the indications for operative urology do not change. Cases of obstructive uropathy demand relief of the obstruction. The presence of foreign substances in the urinary tract demand measures necessary for their removal. None of our cases of urolithiasis derived more than temporary relief and a cure cannot be expected until the calculus is removed, either by operative or non-operative means. On the other hand the utilization of aureomycin in susceptible infective cases favors a better and more permanent result.

One of the "toxic" manifestations which we have observed in several of our cases and which has not been reported by others, was the occurrence of hematuria, frank and microscopic. We think that this finding will be observed by others as experience with aureomycin in genito-urinary tract infections widens. It does not appear that aureomycin is nephrotoxic in any respect, as shown by Harned in his experimental work on dogs; the urine is highly acid, however, during treatment with aureomycin and may remain so for a few days, especially with the higher doses. This acid urine becomes a source of considerable irritation in an enclosed, irritable and inflamed bladder, and it was in our cases of cystitis (in which the acid irritant acted on a sensitive inflamed bladder mucosa) that we found hematuria. Similarly, the highly acid urine was the cause of the bladder discomfort in two of our patients. The discomfort persisted after the discontinuance of the aureomycin. It has been observed that aureomycin is retained in the body and urine longer than other antibiotics.

Summary

1. Aureomycin is effective by mouth in genito-urinary tract infections.

2. Dosage employed in this series was 2 grams on the first day and 1 gram on the second and third days; we recommend, however, a more prolonged therapy of seven to 10 days, on a 1 gram per day maintenance dose.

3. Aureomycin is very useful and effective in penicillin and streptomycin resistant infections.

4. Aureomycin is effective against gram positive cocci and gram negative bacilli, especially against *B. coli* and *Aerobacter aerogenes*, the frequent urinary infective organisms. It is mildly effective against *Pyocyaneus aeruginosa* and ineffectual against *Proteus vulgaris*.

5. In eradicating *B. coli* and *Aerobacter aerogenes* infections, secondary infection with proteus and pyocyaneus very often follows and remains.

6. The results were good, with satisfactory results either of a temporary or of a permanent nature in 20 of our 25 cases.

7. There were very few toxic manifestations. Nausea and vomiting necessitated discontinuance of the drug in only one patient and frank hematuria occurred in another. Both cleared after stoppage of the drug.

8. Hematuria was observed in several cases, and we believe that this was due not to an inherent nephrotoxic action of the drug but to the highly acid urine that occurs in aureomycin treated cases. The hematuria occurred in cases of cystitis where the bladder mucosa was inflamed and irritable.

9. A more extended clinical trial is needed and is in progress.

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TUBERCULOSIS IN B. C. G. VACCINATED NURSES *

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RECENT encouraging reports of B. C. G. vaccination are leading to its more widespread use.[1] The relative protection afforded by B. C. G. vaccination is shown by the experience of Aronson and Palmer with Indians in which the rate per thousand person years was 4.7 in the vaccinated compared to 24.3 in the controls.[2] In Rosenthal's study of vaccination in newborn infants the tuberculosis rate per thousand person years was 1.95 in the vaccinated and 6.46 in the control groups.[3]

That additional protection is necessary for student nurses with negative Mantoux reactions has been shown by the Prophet Tuberculosis Survey of Great Britain. In the study by Marc Daniels, 2 per cent of the positive reactors developed tuberculosis while 6 per cent of the negative reactors developed the disease.[4]

In the first seven years of B. C. G. vaccination at the Cook County Hospital Nursing School, as reported by Rosenthal, there were three cases of pulmonary tuberculosis in 199 controls and one case in 142 vaccinated nurses.[3] Since that report there has been one additional case in the vaccinated group, and three in the control group. Studies of the manifestations of tuberculosis in B. C. G. vaccinated adults are meagre; therefore, the diagnostic problems and the interesting clinical aspects of these cases are presented.

Case 1. This 21 year old student nurse came to the infirmary on the evening of July 25, 1944 complaining of headache and fever which had had a sudden onset at 11:00 o'clock that morning. Her temperature was 102°, the pulse 96 and respirations 16. Except for a few small, non-tender, pea-sized, anterior cervical lymph nodes there were no abnormal physical findings.

She had grown up on a farm in Michigan and had been unusually well. Her only illnesses had been mumps, measles, whooping cough, and a questionable case of smallpox. She entered nurses training in March of 1942. Her first and second strength Mantoux tests were negative, and her chest plate (figure 1) was clear and without calcification. B. C. G. vaccination, by the Rosenthal method,[5] with material prepared by the Tice clinic, was done on March 30, 1942. In May, 1942, her Mantoux was positive, and it remained so at each six month check-up, the last being in May, 1944. Her chest plates remained negative.

Her only illnesses while in training were several bouts of tonsillitis and pharyngitis with cervical adenitis. The weekend before admission, having finished her month's service in the tuberculosis hospital, she visited at home on the farm. She drank milk which was not pasteurized.

For four weeks after admission this patient spiked an evening temperature between 102 and 104.4°, with a relative bradycardia of 80 to 96. Each morning she looked and felt surprisingly well.

Her initial leukocyte count showed a leukopenia of 4000 cells with 61 per cent

* Received for publication August 19, 1948.

polymorphonuclears, 38 per cent lymphocytes, and 1 per cent monocytes. The red cell count was 4.28 million with 14 grams hemoglobin. This hemogram remained relatively constant throughout the illness. Sedimentation rates by Cutler method varied from 40 to 12 mm. per hour.

Ten blood cultures taken at the height of fever were all negative. Urinalyses and urine cultures were negative. Malarial parasites were never seen. Agglutina-

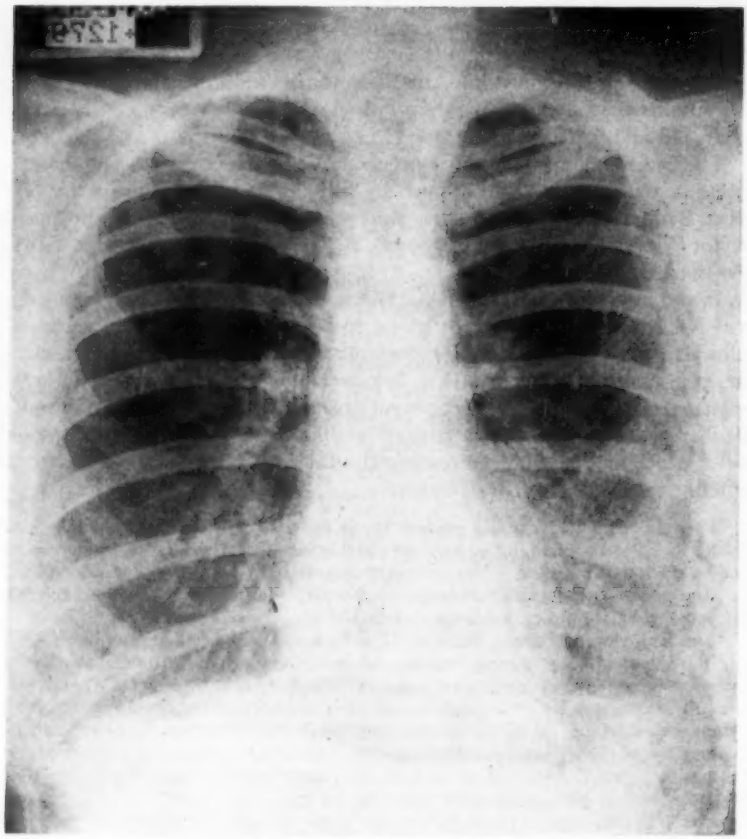

FIG. 1. Case 1; film on entrance to training (September 6, 1942).

tions for typhoid, paratyphoid and brucellosis were negative. Throat cultures and stool cultures were negative.

The chest film on admission showed normal heart and lung fields. Three weeks later check-up film showed an enlarged left hilar node (figure 2). At this time the cervical nodes became slightly more prominent.

At the end of the fourth week the only significant findings had been minimal hilar

and cervical adenopathy, fever, relative bradycardia and leukopenia. At this time the diagnoses considered were undulant fever and Hodgkin's disease. She was placed on sulfamerazine. In the fifth and sixth weeks the temperature fell by lysis. After three afebrile weeks the patient was sent home on September 22, in good health and spirits. She returned to work in December. The cervical glands were barely pal-

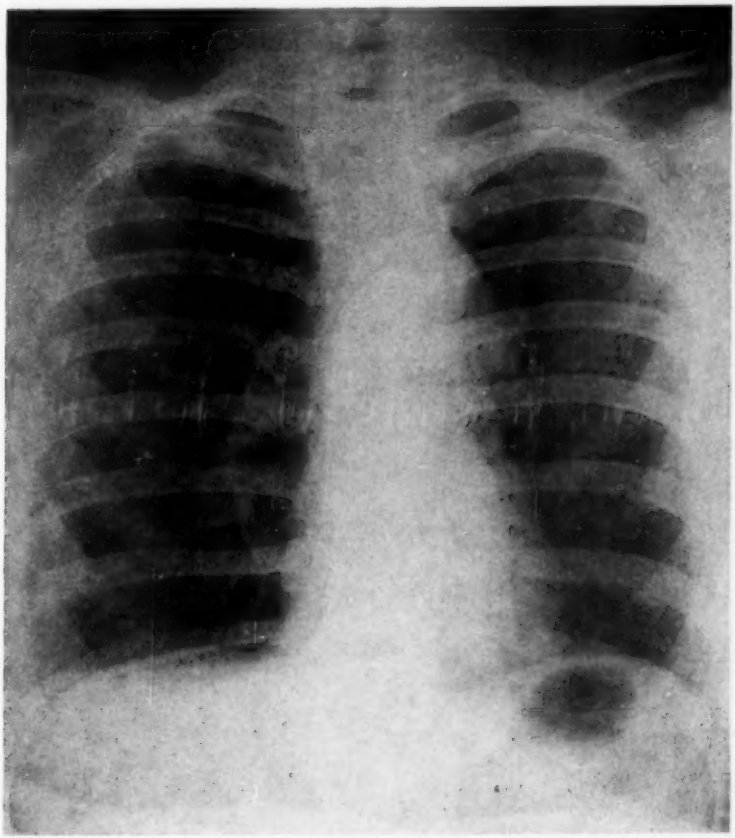

FIG. 2. Case 1; film taken at third week of febrile course (August 26, 1944).

pable and the hilar gland was receding. On routine physical examination in July of 1945, the hilar gland had subsided but one right cervical node had enlarged to the size of a pecan. The gland was biopsied and guinea pig inoculation revealed acid fast bacilli.

A year later the chest film (figure 3) was negative and there were no cervical nodes. In December, 1947, the patient was working and in excellent health.

Case 2. The second student nurse was admitted on February 20, 1948, complaining of chest pain. Four days before she had developed fever and generalized aching and pleuritic pain in the left upper chest. She took aspirin and the fever abated but she continued to have pain. The day before admission she had developed a cough with mucoid sputum.

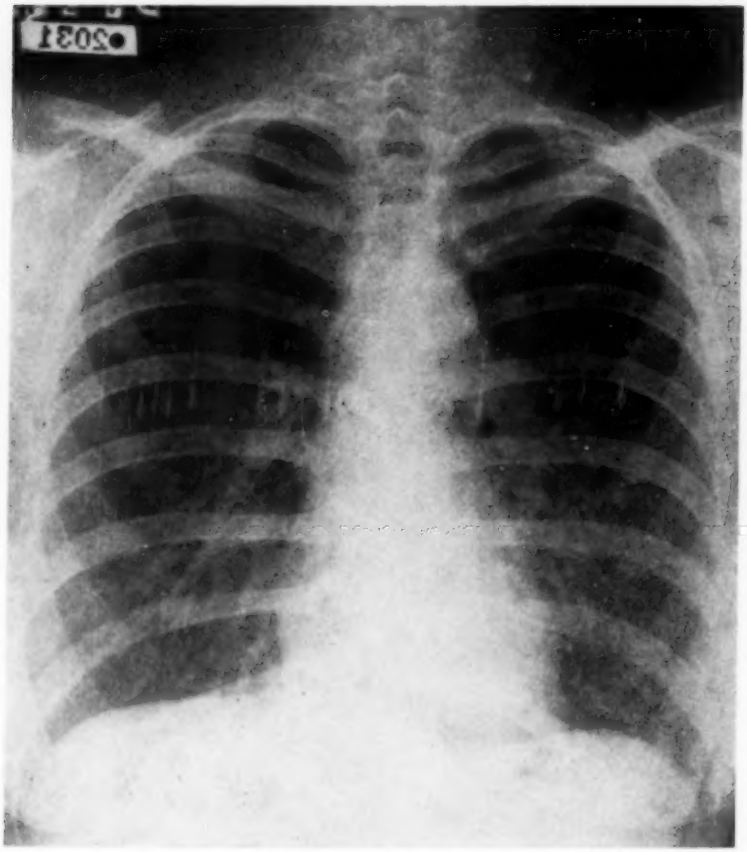

FIG. 3. Case 1; progress film (April 9, 1946).

She was born in Los Angeles, California, and had had chickenpox, whooping cough, measles and mumps. She entered training in September, 1945. The Mantoux test was negative and the chest film (figure 4) revealed no parenchymal lesions or calcification. She received B. C. G. vaccine in October, 1945 and in December the Mantoux had become positive. It remained positive at the six month check-ups, the last being October, 1947. Her only illnesses while in training had been infre-

quent respiratory infections and rubella. She had been working in a tuberculosis ward from January 25 until two weeks before entry.

Physical examination revealed a well developed girl who had lost no weight. The temperature was 100°, the pulse 90, respirations 18. The pharynx was clear and there was no cervical adenopathy. The left side of the chest was splinted, al-

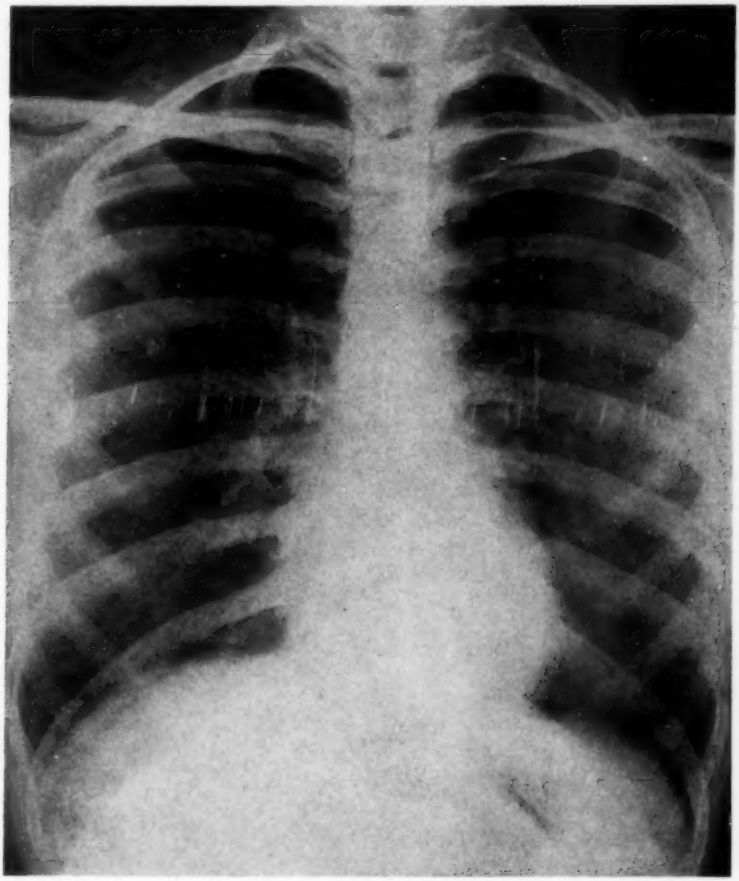

FIG. 4. Case 2; film on entrance to training (June 25, 1945).

though no pleuritic rub or change in breath sounds could be detected. Two days later there was a definite rub. Several days later there was dullness, and moist râles were heard in this area. There were no other significant findings.

Roentgen-ray of the chest revealed a homogeneous circumscribed density in the

upper portion of the left hilum (figure 5). An infiltrative process extended from the right hilum to the right infraclavicular area.

The hemogram showed four million red cells with 12 grams hemoglobin. The white count was 11,900 with 83 per cent polymorphonuclears, 15 per cent lymphocytes and 2 per cent eosinophiles. The sedimentation rate was 25 mm. in one hour. Urinalysis was negative. Sputum examinations were repeatedly positive for tubercle bacilli.

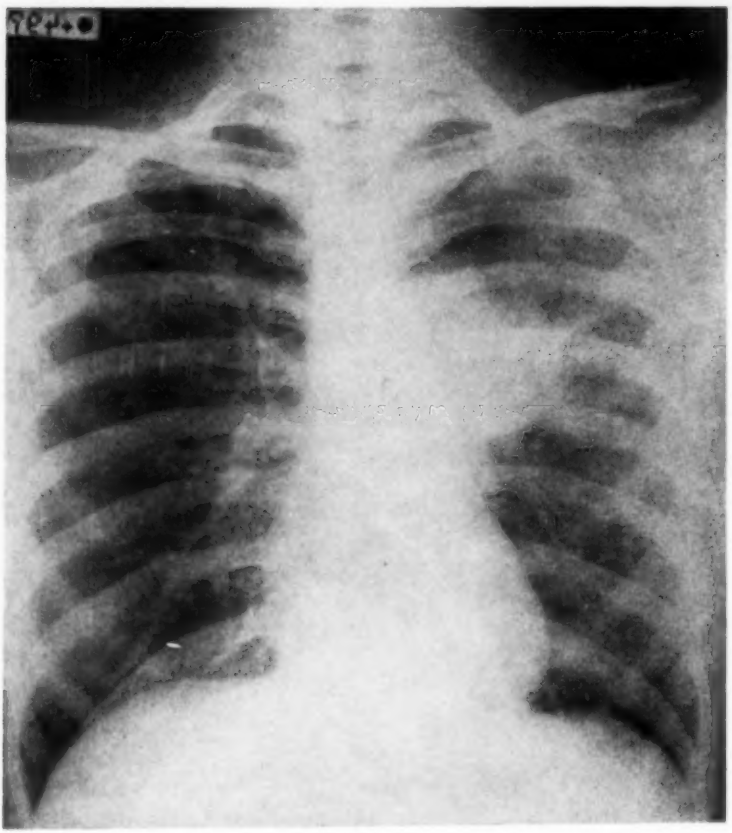

FIG. 5. Case 2; film taken on day of admission (February 20, 1948).

During the first week the pleuritic pain disappeared. The afternoon elevations of temperature became progressively slighter, and in the second month the patient was afebrile. She ate well and gained six pounds. The hilar mass became more circumscribed (figures 6 and 7), and finally the sputums became negative.

Discussion

Both these cases had their onset two years after vaccination—at 27 and 28 months. In Rosenthal's study of newborn infants the highest incidence in the vaccinated group was between two and a half and three and a half years.[5]

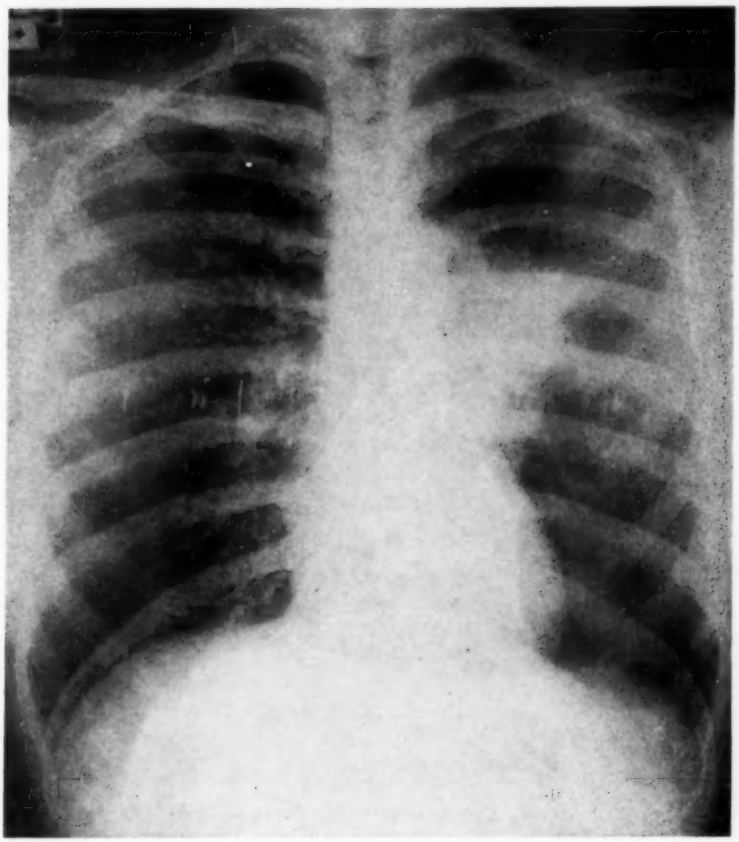

Fig. 6. Case 2; progress film (March 16, 1948).

These cases reëmphasize the risk of exposure in tuberculosis wards. Both of them had explosive onsets after what was presumably a short incubation period—four and six weeks—after the onset of heavy exposure. This almost influenzal onset resembles the outbreak in a Danish school described by Holm.[6]

The clinical courses were interesting. The first case ran a hectic temperature with minimal nodal involvement; the second ran a low grade fever with rather extensive parenchymal and nodal involvement. Both these students showed very little general reaction. They ate well, slept well, felt well, and had no complaints other than impatience with bed rest.

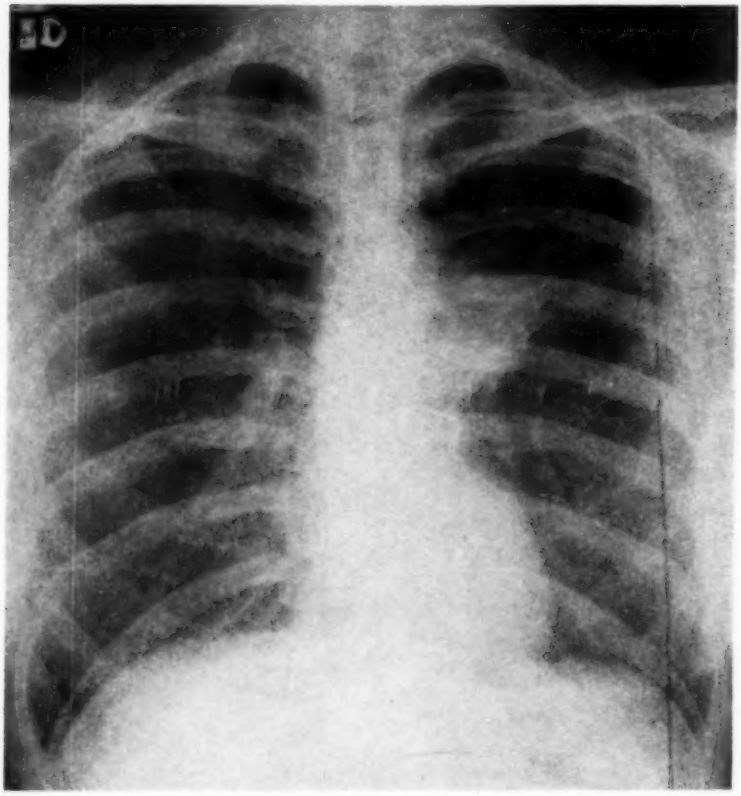

FIG. 7. Case 2; progress film (April 25, 1948).

In both cases lymph node involvement was predominant. It is interesting that at the end of the second year the first case had no calcification.

These cases do not resemble the reinfection type of tuberculosis which we see among our unvaccinated nurses. They suggest that B. C. G. has modified the course of the tuberculous infection.

The difficulty in diagnosis is brought out by the first case where the correct diagnosis was not made for a year.

Conclusion

1. Two cases of tuberculosis developed in B. C. G. vaccinated nurses after heavy exposure on tuberculosis wards.
2. The incubation period was short and the onset explosive.
3. Lymph node involvement was predominant.
4. Clinical courses were relatively benign.

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HYDROTHERAPY IN OSTEOARTHRITIS *

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THE use of hydrotherapy is one of the oldest therapeutic measures in our medical armamentarium. From ancient Greek, Roman and Hindu writings, we find that balneology was highly developed, probably reaching its peak in the declining centuries of the Roman Empire. There is no record, however, that the specific therapeutic indications for the baths were known at that time.[1]

As a result of the many clinical investigations into the etiology and pathogenesis of osteoarthritis, we may conclude that the disease is a degenerative one, hence the terms hypertrophic or degenerative arthritis. For the most part it is a senescent process, whether due to accumulated years or to accelerated aging.

Haden and Warren [2] found that degeneration of the articular cartilage is accelerated by obesity, a lowered metabolic rate, alimentary disturbances, endocrine dysfunction and circulatory inadequacy.[3] The factor of trauma in itself should be emphasized. This trauma may be acute or a result of mechanical stress and strain to the involved joints. For example, the greatest incidence of osteoarthritis of the hands is seen in those doing manual work; likewise, the knees, as weight bearing joints are frequently involved.

No plan of therapy can hope to resolve the cartilagenous and bony degeneration inherent in the disease. By increasing constitutional efficiency, physical therapy can aim to alleviate the predisposing and exciting factors.[4] This will result in either arrest or delay in the process with concomitant relief or alleviation of symptoms. Many therapeutic programs attempt a similar goal, but it is the author's purpose to analyze the rôle of hydrotherapy in the treatment of osteoarthritis.

Our observations and conclusions are based on the use of hydrotherapy for a period of 12 years. During this time, we have treated more than 600 cases of osteoarthritis with physical therapy. In addition, we have made a careful analysis of 200 cases, evaluating their response to hydrotherapy and other means of therapy. It is our conclusion that hydrotherapy is preëminently the treatment of choice; not only in therapeutic results, but also because of low cost and efficiency. More than any other means of treatment, hydrotherapy affords the opportunity of combining passive and/or active exercise and massage during the application of heat.

Before proceeding with a discussion of the method of application, an outline of expected physiological responses to hydrotherapy is indicated. It has been shown in a previous article [5] that hot baths not only cause a temporary rise in basal metabolic rate, but that a series of baths will maintain

* Received for publication September 28, 1948.

this elevation. During the temporary metabolic impetus, proportionate hyperpnea causes large quantities of water vapor to be lost through expired air; concomitantly, carbon dioxide is eliminated in increasing amounts. Injudicious dosage of hydrotherapy may produce an alkalosis, which, if sustained may lead to tetany. This is seen only in patients where treatment is carried to a point simulating heat exhaustion. A single hot bath produces an increase not only in the volume of the urine excreted, but also in the concentration, particularly in the excretion of chlorides. Usually after a series of baths there is better alimentary elimination.

Some osteoarthritics perspire freely from thermal stimulation, while others do not, but after a series of hot baths there is usually an improvement in the function of the sweat glands. When generalized hydrotherapy is applied, a temporary rise in the red blood count and white blood count is observed; there is a negligible rise when hydrotherapy is applied to a single extremity. There is a slight rise in blood pressure which returns gradually to its original level paralleling the return of the body temperature to normal.[5]

The reciprocal reactions of the peripheral and splanchnic vascular beds are well known: increased external temperature and muscular exercise bring about a change in the blood volume ratio in favor of the peripheral structures.

With this foreground of anticipated responses to hydrotherapy, we will proceed to discuss the method of application. As with any other therapeutic program, there can be no definite rule of application. In general, however, it is of the utmost importance that the case be one with osteoarthritic pathologic lesions uncomplicated by infection. For example, in apparent latent cases of infectious arthritis, the patient may suffer a febrile reaction which may increase the amount of already existing damage. In order to avoid serious exacerbations, patients with rheumatoid arthritis, osteoarthritis with superimposed infection, or osteoarthritis with the foci of infection at other points, require an altogether different technic of hydrotherapeutic application.

On several occasions, patients who were clearly osteoarthritics suffered acute exacerbations of apparent latent cholecystitis merely through over zealous application of hydrotherapy. The use of hydrotherapy in combating chronic infections must be based upon the production of reactions, and requires close observation and cautious prescribing in order to achieve encouraging results at all. Hence, prior to hydrotherapy, an afebrile course, a normal sedimentation rate, and a normal filament-nonfilament ratio are used as a guide to the activity of infection. If, by careful history and physical examination, it is unlikely that there will be a flare-up of infection, we proceed with a trial treatment.

Mild cardiac disorders, moderate hypotension, moderate hypertension, or arteriosclerosis do not contraindicate the inauguration of a cautious hydrotherapeutic schedule. We have obtained excellent results in treating patients with osteoarthritis who have recovered from myocardial infarction. The therapy is especially applicable in senile patients, but it is also very

useful in the obese, menopausal osteoarthritics. Hydrotherapy has been used successfully in those patients in whom osteoarthritic pathology follows the later stages of an infectious arthritis when the infection has run its course or has been controlled. Again we might emphasize that in any candidate for hydrotherapy the activity of any infectious process must be carefully evaluated.

Our method of treatment is to place the patient in a tank filled with water at a temperature of approximately 100° F. During the first three to five minutes the temperature of the water is gradually increased to between 103° F. and 106° F., as the condition of the patient indicates, until a rise of about 1° F. in mouth temperature is achieved. The patient is then removed from the tank to a loose blanket pack for about one hour. If during the succeeding 24 hours no reaction occurs, the treatment is repeated at daily intervals, each time raising the mouth temperature to 100° F. or 101° F. If there are no untoward reactions following the first week of treatment, a daily treatment is continued.

When the knees are involved, the patient is maintained in bed without weight bearing until relief from stiffness and pain is achieved. This usually requires about one week in senile patients but often longer in other types of patients. The optimum peak of mouth temperature has been found to be the temperature at which maximum relief from pain, stiffness and spasm occurs. Because of the new found comfort and salutory effects of the bath, the patient is encouraged and enjoys greater muscular relaxation. Reassurance from the attendant is also important at this time, as this encouragement tends to mitigate excitement during the induction period and aids in further relaxing muscle spasm. Manual massage should be confined to very light stroking as deep massage would induce muscular spasm.

Another valuable means of accelerating relaxation in the tank is by the use of turbine agitators which furnish a gentle, even stream of air against the spastic muscles. When the height of relaxation and relief is achieved, the patient is ready to be removed from the water in order to avoid reaching a point of exhaustion or excessive febrile reaction. Before the patient is removed from the tank, the water temperature is lowered by a large thermostatic valve to a temperature cool enough to be exhilarating but not cold enough to induce reflex muscle spasm. This change of water temperature occurs within one to two minutes. During this time the patient is encouraged to exercise under water.

The optimum temperature for underwater exercise varies with the individual; usually the senile and debilitated patients prefer and function better in water temperature between 80° F. and 90° F.; whereas, the optimum temperature in obese patients is usually between 70° F. and 80° F. The relief and relaxation are generally maintained during this period of exercise. Active exercise is preferred. However, if impairment of function is present, passive motion is utilized, always avoiding pain.

It has been found desirable to follow each treatment with general body massage. The fundamental and very important rule for this massage is that pain must be avoided. Patients with flaccid muscles or those in a debilitated state should have only light effleurage (stroking) and petrissage (kneading), and this, in 15 to 20 minute treatments.

The physiologic reaction is intended to be accomplished only by reflex response to this massage. As the muscle tone improves and the individual's tolerance increases, heavier massage is permissible. The period of massage is gradually prolonged to 45 minutes. Only in cases complicated by fibrositis or in advanced osteoarthritic patients where gradual stretching is desired, do we use deep massage to exert a direct mechanical effect.

FIG. 1.

If during the first week of treatment sufficient relief and relaxation of spasm are not accomplished by hot water alone, we frequently precede the treatment with mild sedation, such as aspirin or bromides. The period of underwater exercise must, of course, vary with the strength and condition of the patient. Usually during the first week, five to 10 minutes are all that can be tolerated without undue stiffness the following morning. Thereafter 15 to 20 minutes are allowed. As the joint function and muscle tone improve, other exercises are given to the patient in bed. These are best accomplished under the supervision of a trained technician.

In addition to the symptomatic dietary indications of the patient, it is well to take cognizance of the fact that with this metabolic stimulation, additional calories may be required. This dietary increase should consist not only of greater caloric intake but also a greater protein ratio. Medications are used as indicated. It is also well to mention that in obese individuals who receive thyroid medication, marked reduction in the dosage is usually necessary during a course of treatment.

Throughout the period when weight bearing is not permitted, the knees are exercised by having the feet dangle from the side of the bed. Patients are transported to the tank on a stretcher wagon and hoisted in and out of

FIG. 2.

the tank on a flat stretcher top with a crane (figures 1 and 2). As soon as function without tenderness is restored in the knee joint, a valuable means of regaining muscle power is effected by having the patient ride a stationary bicycle.

The senile patients usually achieve encouraging results within three to four weeks of such institutional therapy. Following ambulation of the patient, it is important to emphasize the elimination of excessive weight bearing trauma, such as stair climbing, inclines, hills, hard pavements, rough terrain, etc. At times a repeat course of hydrotherapy following a rest period of two weeks is necessary. This, however, is the exception. At

home patients usually benefit and maintain their symptomatic improvement by taking daily warm tub baths and by receiving one or two massage treatments each week.

In those cases where such regular after care is not followed, it is often necessary to repeat two to three weeks of hydrotherapy as described, every four to six months. The obese and menopausal patients usually require much longer institutional care depending upon the existing joint pathology and the amount of obesity.[6] These patients usually maintain their benefits under adequate medical supervision and seldom need return for further hydrotherapy. The patients with osteoarthritic pathology subsequent to infectious arthritis are usually treated with hydrotherapy in conjunction with orthopedic measures. The degree of pathologic change as shown by x-ray or found on physical examination may not preclude the restoration of some function if the knee joint can be manipulated under anesthesia satisfactorily, provided there is no extensive eburnation of the joint surface.[7] Cases of *morbus coxae senilis* or other cases where the hip joints are involved seem to respond least well to hydrotherapy.[8]

Summary

The use of hydrotherapy in osteoarthritis provides an extremely valuable adjunct to the medical and orthopedic management of these patients. Judiciously planned courses of treatment, individualized to meet the specific requirement of the patient are valuable in improving or restoring function, as well as combating the predisposing and exciting factors of the disease. Although many cases may be benefited in their homes by improvised applications of the principles set forth, in order to achieve the optimal result institutional care is necessary.

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TULAREMIC PERICARDITIS: A REPORT OF TWO CASES INCLUDING ONE OF CONSTRICTIVE PERICARDITIS *

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Since 1910 when Pearse gave the first clinical description of tularemia,[1] its recognition has become relatively common in certain areas. Despite the proximity of the pericardium to the lungs and pleurae, which are frequently attacked in this disease,[5, 8, 13, 14, 15, 17] it is surprising the pericardium is so rarely involved. Only a few cases of tularemic pericarditis have been reported since Simpson [2] published the first case in 1927. In 1943 Jager and Ransmeier could find only 10 cases, including three unpublished cases and one of their own.[10] A year later Aagaard [12] reported two more, making a total of twelve. With the exception of Jager's one case of chronic constrictive pericarditis, all were of the acute variety with or without effusion. In the present paper two new cases occurring at the University of Virginia Hospital will be discussed and all the previously published cases reviewed. One of the new cases developed constrictive pericarditis requiring a pericardiectomy and the other, although cardiac embarrassment existed for nearly a year, completely recovered.

Case 1. A 13 year old white boy was admitted to the University of Virginia Hospital on February 28, 1948 with the chief complaints of sharp pains in his right chest and shortness of breath.

He had always been in excellent health until about three months before admission when he noted a rather abrupt onset of an harassing non-productive cough, feverishness, and sweating. His illness forced him to bed where he remained until admission. Three weeks prior to hospitalization his cough increased and he developed a sharp, severe pain in the left chest and left upper abdomen accentuated by respiratory movements. Soon he noted the appearance of dyspnea, orthopnea, and nocturia. He consulted his local physician who diagnosed "heart trouble" and prescribed one tablet of digitalis daily. He continued to take this medication until one week before admission when it was discontinued because it did not seem to benefit him. His symptoms continued to increase in severity, consequently his parents consulted another physician who took a roentgenogram of his chest and found a left sided pleural effusion. Because of this he was referred to this hospital for diagnosis and treatment.

He was a poorly nourished and acutely ill white male propped up in bed exhibiting marked dyspnea and orthopnea. His temperature was 101.4° F., pulse 104, respirations 28, and blood pressure 90 mm. Hg systolic and 70 mm. diastolic. There was no evidence of any scars, petechiae, or ulcerations. The mucous membranes were slightly pale. His tonsils were moderately enlarged but not acutely inflamed. There were numerous, small, hard nodes in the left cervical and supraclavicular regions. Examination of his chest revealed dullness, absent tactile fremitus, and absence of breath sounds below the seventh rib posteriorly and the fourth rib

* Received for publication September 7, 1948.

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anteriorly on the left. A few moist râles were heard above this area posteriorly. The heart sounds were distant and a definite to and fro friction rub was heard over the lower precordium synchronously with the heart beat. His heart was enlarged slightly to the left and the aortic second sound was louder than the pulmonic second sound. No edema was present but the liver was tender and extended down four fingers'-breadth below the costal margin.

Laboratory data: On admission he had 4.1 million red blood cells with 62 per cent hemoglobin and 9,100 white blood cells with 59 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes, 14 per cent monocytes, 5 per cent eosinophiles, and 1 per cent basophiles. The urine, blood Wassermann test, and four blood cultures were negative. The blood agglutinations for tularemia were positive in dilution of 1:1280. A Foshay tularemia skin test was strongly positive. Repeated tuberculin skin tests were negative. The venous pressure was 200 mm. of water, circulation time 20 seconds (arm to tongue), and the vital capacity 39 per cent. A sedimentation rate (Bray-Cutler) was 30 mm. in one hour.

The etiology of the patient's illness was not suspected until the tularemic agglutinations were reported positive. Further questioning of his parents revealed he was quite an enthusiastic rabbit hunter. Also just prior to his illness he and his dog had caught a wild rabbit, and he had taken it home for a pet.

An electrocardiogram revealed a P–R interval of 0.14 second, inverted T waves in Leads, I, II, III, VF, V_3, V_4 and V_5 with an upright T in VR. These findings were consistent with a subacute pericarditis with effusion. An x-ray of the chest revealed a pleural effusion on the left and consequently a chest tap was done with the removal of 750 c.c. of a yellowish green fluid. Examination of this fluid showed it had a large weblike clot, a specific gravity of 1.018 and a white cell count of 5,600 with 4 per cent polymorphonuclears and 96 per cent lymphocytes. Culture of this fluid was sterile and all studies for tubercle bacilli were negative. After the fluid was removed kymographic x-ray studies revealed an enlarged heart with greatly diminished pulsations and almost complete absence of motion along the left border of the heart. On fluoroscopic examination almost complete absence of cardiac pulsations throughout was noted. The frontal area of the heart silhouette was 48 per cent larger than that predicted on orthodiagraphy. It was concluded that the kymographic and fluoroscopic findings were also consistent with a pericardial effusion.

Course in the hospital: In the next two months the patient had many changing signs and laboratory findings. He was digitalized, put on a low sodium diet, given mercupurin, and frequent chest taps were done, all of which added to his comfort. The pericardial friction rub persisted for four or five days, then disappeared but his dyspnea persisted and edema developed. For the first nine days he was maintained on maximum doses of salicylates, but in spite of this he ran a low grade fever. However, when this was discontinued his fever rose to 102° F. On the eleventh hospital day he was started on two grams of streptomycin daily which was later reduced to one gram daily. On this antibiotic his temperature gradually subsided to normal over a 10 day period. His pulse remained rapid and the venous pressure rose to about 240 mm. of water. A narrowed pulse pressure was persistently found with blood pressures averaging about 85/70. Repeated electrocardiographic studies showed changes consistent with a subacute pericarditis and digitalis effect. The P–R interval ranged from 0.14 to 0.19 second which was considered a nonspecific change. The tularemic agglutination titers continued to rise through the third hospital week and can be found in table 1.

During the second and third weeks of his hospitalization three pericardial taps were done. The amount of the fluid obtained by the first tap was indeterminate as it was mixed with pleural fluid but on the second, 75 c.c. of a straw colored fluid were obtained. Following this tap air was injected into the pericardial sac where it was

demonstrated by x-ray. On the third tap only 12 c.c. of fluid could be obtained. The fluid obtained on these taps was cultured for *Past. tularensis* but was negative. Also, some fluid from the first tap was injected into a guinea pig which developed no positive findings for tularemia. Repeated cultures of the pleural fluid for *Past. tularensis* were likewise negative. Unfortunately, these cultures were made after the patient had been started on streptomycin. Both the pericardial and pleural fluids showed positive agglutinations for tularemia (table 1). As a matter of interest the streptomycin level was determined in the pericardial fluid, pleural fluid, and the blood at about the same time and each revealed one unit per c.c. After the removal of the effusions streptomycin was injected into the pleural and pericardial sacs.

By the sixth week of hospitalization it was felt that a constrictive pericarditis had developed. The signs of cardiac embarrassment persisted. Repeated fluoroscopic examinations showed a cardiac shadow that had gradually decreased in size until it remained constant and with almost complete absence of pulsations. The sedimentation rate had fallen to normal and the white blood count remained about 10,000 with a normal differential smear. Streptomycin was discontinued on the forty-seventh day. Ten days later, because he continued to have distressing symptoms of dyspnea, orthopnea and edema, it was felt that a pericardial resection would be necessary.

TABLE I

Tularemic Agglutination Titers during Hospitalization

Approximate week of illness	12		13		14		22	
Week of hospitalization	1		2		3		10	
Agglutination	Complete	Incomplete	Complete	Incomplete	Complete	Incomplete	Complete	Incomplete
Blood (serum)	1:160	1:1280	1:1280	?	1:1280	1:5120	1:320	1:2580
Pericardial Fluid	—	—	1:160	1:1280	1:320	1:1280	—	—
Pleural Fluid	—	—	1:80	1:640	—	—	—	—

On the fifty-seventh hospital day an operation revealed a constrictive pericarditis and a pericardiectomy was done. The pericardium was found to be greatly thickened with a thick layer of organized fibrin between the pericardium and epicardium. A large area of the anterior pericardium and a considerable portion of the left lateral pericardium were resected. The tissue adjacent to the epicardium over the same area was likewise removed. Following this operative release of the constriction, the heart bulged up into the operative site and the pulsations improved dramatically. Immediately following the operation the patient did well, but in the next two or three days he required an oxygen tent and frequent chest taps. After this, however, he improved gradually but progressively.

The microscopic pathological report of the tissue removed at operation was as follows: "Sections of the pericardium show that it is composed of fairly dense fibrous connective tissue which contains a moderate diffuse infiltration of leukocytes chiefly lymphocytes. The fibrous connective tissue shows some hyaline changes. Sections of the tissue adjacent to the epicardium demonstrate a similar fibrosis but the leukocytic infiltration is more marked and shows a tendency toward focal grouping. Numerous giant cells are seen. In addition the stroma demonstrates congestion, edema, and hemorrhage. Within some of the fields studied there is granulation tissue formation. Special stains for acid fast organisms were negative."

Following surgery his venous pressure fell to 120 mm. of water and an orthodiagram revealed a notable enlargement of the cardiac shadow with excellent pulsations. The enlargement of the liver regressed and the patient became completely asymptomatic.

The patient was discharged on May 13, 1948 and was followed in the Out-Patient Department. On return visits he was completely asymptomatic and had resumed full activities. Subsequent physical examinations showed no evidence of any cardiac embarrassment and the heart sounds were normal. Six weeks after discharge a chest x-ray was entirely normal, and fluoroscopic studies revealed that his heart size had returned to normal and the pulsations were excellent. When last seen, four months after discharge, he was in excellent health and was returning to school.

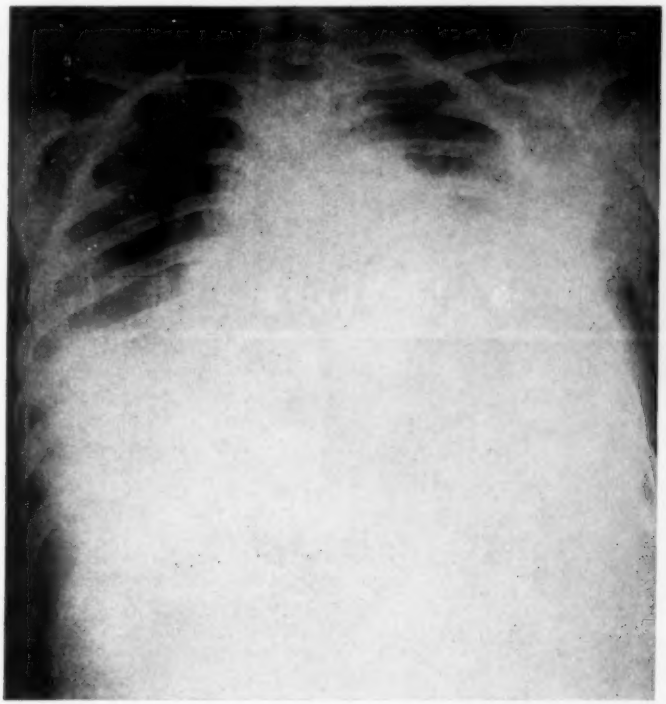

FIG. 1. X-ray of the chest of Case 1 showing enlarged cardiac shadow and pleural fluid.

Case 2. A 30 year old white truck driver was admitted to the University of Virginia Hospital on August 25, 1940 with complaints of a pain in his left chest, exertional dyspnea, and weight loss of 20 pounds.

Nine months prior to admission he and his father-in-law had skinned a rabbit. Within three days both were seized with a fulminating illness which resulted in the death of his father-in-law three days later. The patient was hospitalized in Washington, D. C. for 22 days with a severe illness which ran a febrile course. During this period he had a very harassing cough productive of mucoid sputum from which

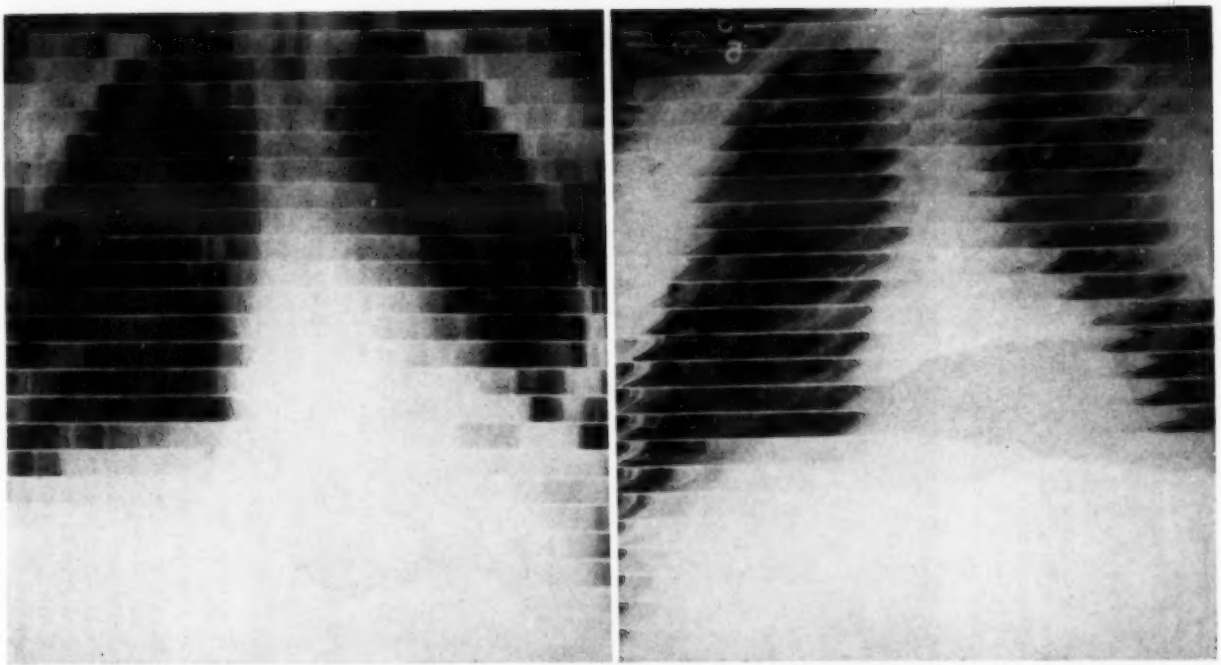

FIG. 2. Kymographic x-rays of Case 1 before and after pericardiectomy. Before surgery (left) virtually no cardiac pulsations could be seen, but after removal of the constricting pericardium (right) excellent pulsations were present.

Past. tularensis was recovered by inoculation into a guinea pig. An x-ray of the chest showed areas of pneumonia in both bases and a small amount of fluid on the right. A chest tap was done and the fluid likewise yielded *Past. tularensis* on animal inoculation.* Following discharge from the hospital, he had a prolonged convalescence lasting three months.

About six weeks previous to admission to the University of Virginia Hospital he developed epigastric fullness, anorexia, and a persistent cough productive of whitish sputum. Soon he began to have a dull aching pain in the left upper chest radiating to the left shoulder which was made worse at times by deep respiration. Exertional dyspnea and weakness appeared and three weeks before admission he began to have night sweats, chills, and a fever varying between 100° F. and 102° F. His physician saw him about two weeks prior to admission and found a rapid pulse, fever, and a pericardial friction rub. He obtained a chest x-ray which showed cardiac silhouette enlargement over that taken nine months before. Hospitalization was advised for diagnostic studies. There was no history of orthopnea, nocturia, edema, nor hemoptysis, but there was a 20 pound weight loss.

On physical examination he was an asthenic male with a temperature of 101.8° F., pulse 100, respirations 22, and blood pressure 100/70. His fingers and feet were slightly cyanotic. A few fine crackling râles were heard over the right lower lung posteriorly. His heart was enlarged slightly to the left. The heart sounds were quite muffled and a to and fro pericardial friction rub was heard best along the left lower border of the sternum.

Laboratory studies were as follows: The urinalysis, red blood count, hemoglobin, white blood count and a differential smear were normal. Agglutinations with *Past. tularensis* were strongly positive in the 1:1280 dilution. A sedimentation rate was 29 mm. in one hour. Repeated blood cultures were negative. Blood serology and tuberculin skin test were negative. The circulation time (arm to tongue) was 12 seconds and the venous pressure was 50 mm. of water.

A seven foot chest film showed the lung fields to be clear but the heart shadow was enlarged both to the right and to the left. Under the fluoroscopic screen only feeble cardiac pulsations were noted. An electrocardiogram showed inversion of the T wave in I and II with a flat T in III which were consistent with an acute or chronic pericarditis. On orthodiagraphy a 31 per cent enlargement of the cardiac shadow over that predicted for the patient was found.

In the hospital the patient ran a septic course with afternoon temperatures rising to approximately 102° F. for the first 10 days, then gradually subsiding to normal. Cardiac fluoroscopy two weeks after admission showed noticeably weaker pulsations of the heart consistent with a pericardial effusion or possibly a developing constrictive pericarditis. A chest film demonstrated further enlargement of the cardiac silhouette, and three pockets of fluid were visible in the right chest and a small effusion was present on the left. Gradually the pericardial friction rub disappeared and the heart sounds became more distant. The venous pressure began to rise until by the third week it was 220 mm. of water, where it remained until the time of discharge. There was also some narrowing of the pulse pressure. In spite of the evidence that a pericardial effusion was present, no fluid could be aspirated when a pericardial tap was attempted. Another chest film six weeks after admission showed larger amounts of fluid in the right chest but a smaller cardiac shadow. However, on repeated chest taps no fluid could be obtained. The patient was discharged after 54 days of hospitalization and the only symptom at discharge was moderate exertional dyspnea. The final diagnoses were tularemia, tularemic pericarditis with effusion, and possible developing constrictive pericarditis.

* Courtesy Dr. Austin B. Chinn, Washington, D. C.

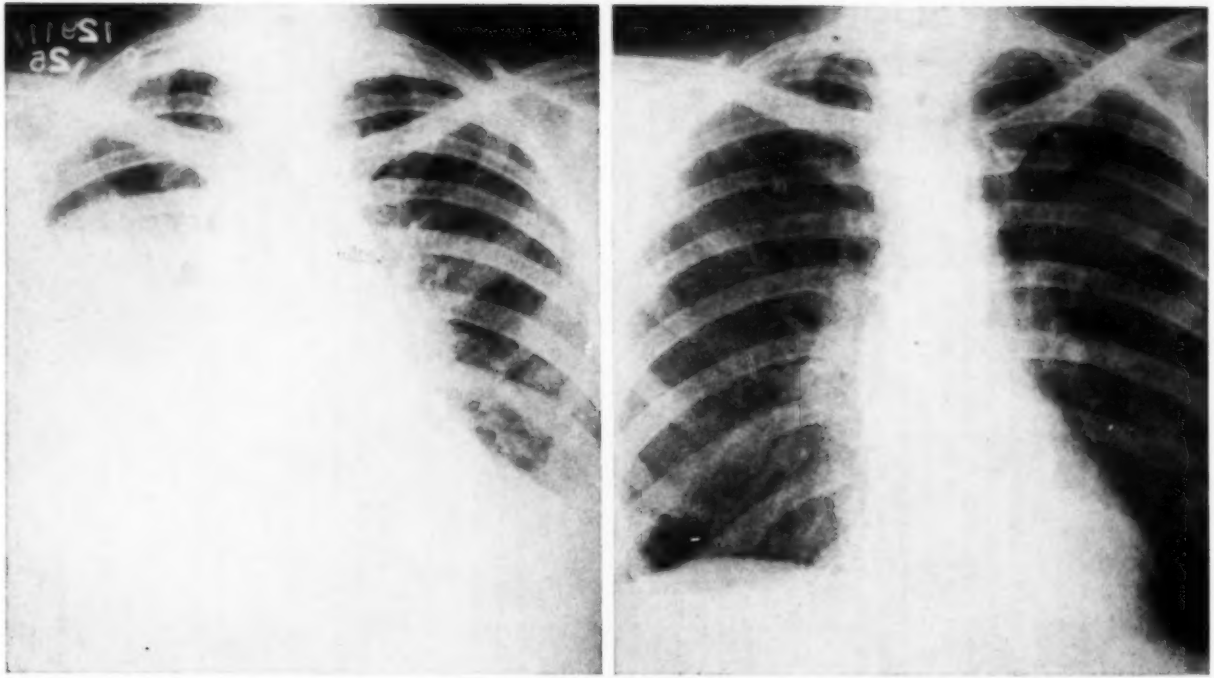

FIG. 3. Chest x-rays of Case 2 during the first admission (left) and one taken seven years later (right) showing practically a normal chest.

The patient was seen several times in the Out-Patient Department in the next four months. He continued to have dyspnea on exertion and developed slight dependent edema. Fluoroscopic studies showed essentially the same findings as on discharge with the exception of a small increase in the amount of fluid in the right chest pockets.

The patient was readmitted on March 1, 1941 for reëvaluation. A physical examination at this time revealed a well nourished male with a normal temperature, pulse, respiration, and blood pressure of 150/78. There was a moderate degree of venous distention of the neck. Dullness was present all over the right chest anteriorly and posteriorly except at the apex. Over this same area there were noted a suppression of breath sounds and whispered voice, and absent tactile fremitus. The cardiac apex was percussed approximately 1.5 cm. outside the mid-clavicular line and the heart sounds were distant except at the apex. A slightly tender liver was palpated two fingers'-breadth below the costal margin, and a moderate amount of brawny ankle edema was present.

Urinalysis, hemoglobin, white blood count, smear and sedimentation rate were normal. Agglutinations with *Past. tularensis* were positive to the 1:1280 dilution. A tuberculin skin test was negative. Venous pressures ranged between 180 and 200 mm. of water and the circulation time was 53 seconds.

A chest film showed the same three pockets on the right. On two occasions 250 c.c. of a clear, straw colored fluid were removed from these pockets. Guinea pig inoculation of this fluid gave no evidence of tularemia. Tularemic agglutinations of this fluid were positive at the 1:160 level. Kymographic x-ray studies demonstrated normal cardiac pulsations and the diagnosis of constrictive pericarditis was thought to be excluded. He was discharged after two weeks with no particular improvement and was advised to curtail his activities.

The patient was instructed to return to the Out-Patient Department but he failed to do so. After the diagnosis of tularemic pericarditis was made in the preceding case, the record of this patient was reviewed. He was located again with difficulty, after this seven year period, and he returned to the Out-Patient Department for follow-up studies on July 13, 1948. He stated that following discharge his symptoms gradually subsided over several months and that he had been asymptomatic and in excellent health since. A physical examination on his return was entirely negative and a chest fluoroscopy showed a normal size heart with excellent pulsations except for possibly a slight diminution in the amplitude of the right side of the heart. A chest x-ray showed complete clearing of the pleural fluid and all that remained was a small area of pleural thickening in the right chest. An electrocardiogram showed negative T waves in Leads I, II, III, and V_4 which were consistent with an old healed pericarditis. Tularemic agglutinations of his blood serum were positive in the 1:2560 dilution.

The final diagnoses were tularemia, tularemic pericarditis with effusion, and tularemic pleural effusion. Although the development of constrictive pericarditis was suspected at one time, this diagnosis was disproved by subsequent studies.

Discussion

As the neighboring lungs and pleurae are so frequently involved in tularemia, it is amazing that the pericardium is so seldom invaded. There have been only 14 cases of tularemic pericarditis published including the two of this report while the cases with pleuropulmonary manifestations have been numerous. The pertinent points in the diagnostic criteria of the previously reported cases of tularemic pericarditis as well as those of this paper are summarized in table 2.

TABLE II

An Analysis of the Evidence of the 14 Cases of Tularemic Pericarditis

Case Age, Sex	Ext. Les.	Pneu.	Pl. Eff.	Rub	Other Signs of Pericarditis	Peri. Tap	EKG	X-Ray Peri. Eff.	Organism	Agglutinations	Follow-up (Autopsy Findings if Died)
I. (2) M. 37	U.G.	? None	None	Yes	Precordial pain, dyspnea	Yes	—	Yes	—	1:60	Recovered
II. (3) F. 35	None	LUL LLL	Bilat.	Yes	Distant and weak heart sounds, ascites, upper abdominal pain, glossitis and stomatitis	—	—	Yes	—	1:320—20 d. 1:5,120—64 d.	Died 64 d. Fibrinous pericarditis with effusion, pneu. LUL, foci necrosis lungs, liver, etc.
III. (4) F. 29	U.G.	Left	Left	Yes	Pain in chest, distant heart sounds, dyspnea, enlarged heart	—	Yes	Yes	—	0–15 d. 1:1280—19 d.	Recovered completely
IV. (7) M. 42	None	LLL	Left? dry tap	Yes	Precordial pain, dyspnea, thready pulse, faint heart sounds, cyanosis	—	Yes	—	—	1:160—14 d. 1:5120—47 d.	Recovered completely
V. (6, 11) F. 47	U.G.	All lobes Bilat.	Bilat.	None	None. No signs of heart failure; aortic stenosis, auricular fibrillation	—	—	—	Yes Spleen	0	Died 19 d. Sm. area fibrinous pericarditis, pneu. bilat., focal necrosis lungs, liver, spleen. Myocardial Aschoff bodies. Bilateral pleural effusion
VI. (9)	None	?	Left	Yes	Dyspnea, cardiac enlargement, edema, epigastric pains, and tenderness	—	Yes	Yes	—	1:80—13 wk.	Recovered ?
VII. (10)	?None Nasal Septal Ulcer	RML LUL	Right	Yes	Tachycardia	—	—	—	Yes Lung	0–7 d. 1:1280—13 d.	Died 13 d. Rt. fibrinous pleuropericarditis, pneu. LUL and RML with cavitation, pulmonary edema, peritonitis
VIII. (10) M. 69	U.G.	LLL	Left	Yes	None	—	—	—	—	1:20—25 d.	Recovered? No follow-up

TABLE II—*Continued*

Case Age, Sex	Ext. Les.	Pneu.	Pl. Eff.	Rub	Other Signs of Pericarditis	Peri. Tap	EKG	X-Ray Peri. Eff.	Organism	Agglutinations	Follow-up (Autopsy Findings if Died)
IX. (10) M. 34	U.G.	Bilat.	Bilat.	Yes	Distant ht. sounds, paradoxical pulse, distended neck veins, dyspnea, orthopnea, ascites, RUQ tenderness, cyanosis	—	—	—	Yes Ulcer and Blood	0—several times	Died 9 d. No autopsy
X. (10) M. 22	None	Right	Bilat.	Yes	Dyspnea, cardiac enlargement, distant ht. sounds, paradoxical pulse, edema, tachycardia, ascites, elevated venous pressure	Yes	Yes	Yes	Yes P.F.	1:160—77 d. 1:1280—98 d.	Developed constrictive pericarditis with persistent cardiac embarrassment
XI. (12)	None	Left	Left	Yes	None except tachycardia	—	Sl. QRS	—	Yes Blood P.F.	1:160—2 wk. 1:320—4 wk.	Recovered
XII. (12)	None	Right	Right	Yes	Edema, orthopnea, and dyspnea	—	Yes	Yes	Yes P.F.	1:2560	Recovered
XIII. (A) M. 30	None	Bilat.	Bilat. chiefly right	Yes	Muffled ht. sounds, dyspnea, edema, distended neck veins, enlarged liver	Dry Tap	Yes	Yes	Yes P.F. and Sputum	1:1280—9 mo. 1:2560—7 yrs.	Gradual subsidence of cardiac embarrassment with complete recovery
XIV. (A) M. 13	None	Left?	Left	Yes	Distant ht. sounds, dyspnea, orthopnea, edema, distended neck veins, tachycardia, elevated venous pressure	Yes	Yes	Yes Dev. Constr. Peri-carditis	—	1:1280—3 mo.	Treated with streptomycin. Pericardiectomy on 57th hospital day with complete recovery

Symbols: 1. Negative or not reported
2. Rub—pericardial friction rub
3. U.G.—ulceroglander
4. d.—day or days
5. wk.—week
6. P.F.—pleural fluid
7. mo.—month
8. ( ) reference number
9. A—author
10. P.—pleural
11. Les.—lesion
12. Eff.—effusion
13. Peri.—pericardial

The diagnosis of tularemia may usually be made with relative ease with a typical history, and it should also be suspected in an atypical pneumonia with history of contact with rabbits. This diagnosis can be confirmed with positive agglutinations for *Past. tularensis*, especially with rising titers.[7, 9, 18] The intradermal skin test is diagnostic if it becomes positive and a positive test is said by Foshay to develop frequently in the first week of illness.[7] Both agglutinations and skin test remain positive for life. Recovery of the organism either by culture or animal inoculation establishes the absolute diagnosis, but these procedures are not without danger to the laboratory worker. In this group of 14 cases 12 had positive agglutinations with two patients dying before they had become positive. In seven the diagnosis was established by agglutinations alone, while in the remaining seven the organism was recovered. It is also interesting to note that in only five patients was the classical ulceroglander lesion seen.

The diagnostic criteria for pericarditis in these cases depended chiefly on the demonstration of a pericardial friction rub which was heard in 13 patients. Electrocardiographic changes were consistent with this diagnosis in seven cases. Pericardial effusions were demonstrated by muffled or distant heart sounds, evidences of fluid by chest film, cardiac kymography, fluoroscopy, or pericardial taps in eight patients. Temporary cardiac embarrassment was observed in eight with acute pericarditis and was manifested by such signs as distended neck veins, elevated venous pressure, orthopnea, dyspnea, enlarged liver, ascites, nocturia, and edema. These signs were also present in the two cases that developed chronic constrictive pericarditis.

The diagnosis of chronic constrictive pericarditis in Jager's case was confirmed by x-ray, electrocardiography, pericardial tap with the recovery of the organism, and injection of air into the pericardial sac demonstrating a greatly thickened pericardium by x-ray. In the case of constrictive pericarditis reported in this paper, the diagnosis was confirmed by rising agglutination titers, x-ray, fluoroscopy, kymography, pericardial taps, electrocardiography, and pericardiectomy. With the etiology of these two cases proved, this disease should be added to the list of unusual causes of constrictive pericarditis.

Pleuropulmonary manifestations were noted in all but one case. Thirteen had a pleural effusion and 11 had tularemic pneumonia. In the three cases without definite evidence of pneumonia, it was probable that it had been present from their histories. The high incidence of pleuropulmonary lesions in this series suggests that tularemic pericarditis develops only in the presence of these lesions.

Case 1 of this report is the first case of tularemic pericarditis treated with streptomycin to be reported. In spite of its apparently beneficial effect streptomycin did not prevent the development of constrictive pericarditis. However, it was not started until late, in the fourth month of illness. Surgical removal of the constricting pericardium completely relieved the in-

capacitating symptoms. The second case is quite interesting in that at the time of the first admission constrictive pericarditis was considered highly probable, but no evidence of this could be found seven years later.

This series is too small to warrant any statistical conclusions, but with four deaths in 14 cases the mortality rate was about 28 per cent, which is about the same mortality rate as that reported by Blackford and Casey for tularemic pneumonia.[8]

SUMMARY

Two cases of pericarditis due to tularemia have been presented. In one constrictive pericarditis developed requiring a pericardiectomy for the relief of symptoms and the other, although tularemic pericarditis with effusion developed and cardiac embarrassment existed for almost a year, recovered completely. Also, a brief analysis of the previously published cases has been made.

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THE CARDIOINHIBITORY CAROTID SINUS SYNDROME *

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OF interest for years as a readily demonstrable etiologic factor in certain cases of syncopal or convulsive attacks, the cardioinhibitory carotid sinus syndrome has itself fallen under suspicion as a manifestation of myocardial disease. This report concerns 11 unselected patients seen by the author within the past year and a half whose presenting complaint was fainting or giddiness and whose symptoms were reproduced by mechanical stimulation of the carotid sinus. A review of the literature, pertinent if not exhaustive, will be attempted before presentation of the cases.

SYMPTOMS

Clinical differentiation of carotid sinus hypersensitivity as a cause of syncope was popularized by the observations of Weiss and his coworkers [1, 2] two of whose later papers will be discussed here; though a full description of the anatomy and physiologic activity of the carotid sinuses had been written earlier by Hering.[3] Dizziness, weakness, ringing in the ears, even epigastric distress may precede periods of unconsciousness lasting one to three minutes. Convulsive phenomena were observed in 13 of Weiss's 17 patients.[1] Hyperpnea and pallor during an attack are usual. The patient, as a rule, feels entirely well following a seizure; in only one case of Weiss's was weakness for a day or more reported.

Factors precipitating seizures, as emphasized by Weiss, include tight collars, shaving, turning the head, blows on the neck, anything, in short, which tends to exert direct pressure on the carotid sinus area. Later authors, however, have found a definite precipitating factor in only a minority of cases; Smith, for example, elicited a positive history in only 25 per cent of his 35 cases.[4] A review of 59 cases reported in detail during the past decade discloses a precipitating factor in 18 (30 per cent), most commonly sudden movement of the head and neck, sometimes a change from the supine to the erect position, coughing, or straining at stool.[5-21]

SIGNS

Direct pressure over the carotid sinus which reproduces the patient's symptomatology and causes distinctive changes in heart rate is the only valid basis for diagnosing cardioinhibitory carotid sinus syndrome.[22] As illustrated by Askey,[23] a suitable technic is to seat the patient upright, feel for the bifurcation of the common carotid artery, which will usually be

* Received for publication June 24, 1948.

found as a small bulbous enlargement below the angle of the jaw at the level of the superior margin of the thyroid cartilage, and exert steady pressure against the spinal column for 10 to 15 seconds. Unduly prolonged stimulation, especially if continued during syncope, may be fatal.[13] Failure to seat the patient upright greatly diminishes the patient's response.[24] Massage is to be avoided [22]; simultaneous bilateral carotid sinus stimulation may be dangerous.[1]

The results of carotid sinus stimulation may be divided into several categories, the subjective sensations related by the patient, the general phenomena observed by the examiner, and the specific effect upon the circulation recorded by precise instruments. The first may include the giddiness, blurring of vision, sour taste in the mouth, and other sensations, including loss of consciousness, which have characterized spontaneous attacks. Secondly, the examiner may note pallor, sweating, deepened but not accelerated respirations,[25] stare, unconsciousness, and twitching or convulsive movements of the face or extremities. The circulatory effects, most significant for our consideration, will be dealt with separately.

Circulatory Changes

Weiss et al.[2] early found that circulatory responses to carotid sinus stimulation were divisible into three types. The first, found in 19 (34 per cent) of 56 cases, was characterized by cardiac asystole, an effect which, abolished by atropine, was dubbed vagal (cardioinhibitory to succeeding writers). The second, seen in three of 56 cases (5 per cent), showed a drop in blood pressure without significant alteration of pulse rate; this, abolished by epinephrine through direction effect upon blood vessels, was called depressor (vasodepressor). Lastly, a large number of patients (34 out of 56 or 60 per cent) lost consciousness despite the maintenance of normal pulse rate and blood pressure, a variation termed by Weiss cerebral (central). Subsequent reports have brought out the frequency of the first, our present concern.

As a criterion for the diagnosis of carotid sinus hypersensitivity Nathanson [22] has postulated cardiac standstill of 5 seconds, but Sigler [14] has devised the following degrees of response: +, 10 per cent slowing of cardiac rate; ++, 10 to 30 per cent slowing; +++, 30 to 70 per cent slowing; ++++, 3 second cardiac standstill. Either of the last two responses he calls "marked." Responses other than asystole may be recorded on a simultaneous electrocardiogram, principally sino-auricular slowing, varying degrees of auriculo-ventricular block, and ventricular ectopic beats.[26, 15, 27] The type of response depends, among other things, on the distribution of cardiac innervation to rhythmic foci, the sinus node being influenced primarily by the vagus, and rhythmic activity of ectopic centers.[27]

Factors Influencing the Circulatory Response

Sex: Many authors have stressed the predominance of the male sex in all series of carotid sinus hypersensitivity, the percentages ranging from 85

per cent [22] to 94 per cent.[4] In reviewing 59 cases of carotid sinus syndrome reported in detail,[5, 21] the author found 51 to involve males (86.5 per cent).

Age: The older age groups contain far more hyperreactors. Of Nathanson's 115 cases, 70 per cent were between 50 and 70 years of age; all were over 30.[22] Sigler,[28] testing 1,151 males and 735 females, found that of the former 31.4 per cent of those less than 20 years of age showed a positive response to carotid sinus pressure; 28.3 per cent of those between 21 and 30; 81.2 per cent, from 31 to 40; 90.6 per cent, from 41 to 50; 90 per cent, from 51 to 60; and 87 per cent, over 60. The figures for females were, for the respective age groups, 55.6 per cent, 48.7 per cent, 63.3 per cent, 63.7 per cent, 72.8 per cent, and 67.5 per cent. Of 59 cases of carotid sinus syndrome,[5-21] two were in the third decade; four in the fourth; six in the fifth; 20 in the sixth; 21 in the seventh; and five in the eighth.

Drugs: The effects of various drugs on carotid sinus sensitivity will merely be listed here. The following familiar drugs accentuate vagal type hypersensitivity, mecholyl, digitalis, nitrites,[2] caffeine, calcium gluconate, and niacin.[27] On the opposite side are atropine, belladonna, epinephrine, ephedrine, alcohol,[27] and quinidine [2] which diminish or abolish the manifestations of vagal type hypersensitivity.

Local Abnormality, Including Arteriosclerosis: Earlier authors tended to emphasize local pressure on the carotid sinus, as by lymph nodes in cervical adenitis, or peripheral arteriosclerosis rendering external pressure more readily transmitted to receptors within the carotid sheath.[2] Later reports, however, depreciate the influence of afferent receptors and hence of local factors in the production of carotid sinus hypersensitivity.[22, 28] If the two main circulatory effects of hypersensitivity, cardioinhibitory and vasodepressor, are equal in degree, says Nathanson,[22] then afferent receptors must be responsible, since the effector organ is in one case, the heart, and in the other, the smaller blood vessels. In 12 patients with cardiac standstill in response to mechanical pressure of 6 seconds, an effect abolished by intravenous atropine, there was an average blood pressure drop of only 15 mm. of mercury; hence, the latter effect does not compare in intensity with the former. Afferent pathways, then, are excluded as the site of sensitivity of the cardioinhibitory reflex, leaving hypersensitivity of the vagus as the explanation. Furthermore, as Sigler points out,[28] the greater effect of mechanical pressure when the patient is upright is against a purely local theory, as is the clinical finding that many patients with local arteriosclerosis do not have carotid sinus hypersensitivity. The author, in reviewing the aforementioned 59 detailed case reports, found peripheral arteriosclerosis mentioned in only six; one case [12] had inflammatory lymph nodes in the carotid sheath.

Heart Disease: Angina pectoris, typical in the character and intensity of pain, radiation, and responses to nitrites, but not related to effort was described by Weiss and his coworkers in association with the carotid sinus

syndrome.[2] Friedman [19] has described the anginal syndrome as a manifestation of hyperactivity of the carotid sinus. Sigler believes the converse [14]; high degrees of carotid sinus hyperactivity, he says, occur very rarely in the absence of coronary disease. Sigler divided 1,886 patients into four groups: (1) those with demonstrable coronary sclerosis; (2) those with demonstrable hypertension but without coronary sclerosis; (3) those with cardiac disease other than arteriosclerotic; and (4) those with no cardiac disease. He [28] found that approximately 93 per cent of the first group showed significant bradycardia in response to carotid sinus pressure, and that in 70 per cent of this number the response was of grade 3 or more intensity (see above). The percentages of positive responses in the other groups were 75, 79, and 55 respectively, and the grade of response in each was much lower. Thirty-four of Nathanson's first 40 patients having cardiac standstill in response to mechanical carotid sinus pressure showed evidence of coronary disease of the anginal type.[27] One-third of the patients with coronary disease and angina were hyperreactors. Nathanson, as we have seen,[22] attributes the cardioinhibitory type of response to hypersensitivity of the vagus; Sigler [28] believes that resistance to vagal impulses is lost at the synapses within the heart muscle. Local ischemia, he continues elsewhere,[14] either diminishes the resistance of ganglions and myoneural junctions in the heart or produces local chemical changes that sensitize the vagus system in the heart. Whatever the explanation, it is of interest to note that of the 59 cases of carotid sinus syndrome reported in detail,[5-21] 28 (47.5 per cent) showed evidence of arteriosclerotic or hypertensive cardiovascular disease.

Biliary Tract Disease: That factors other than coronary disease cause increased sensitivity of the carotid sinus has been suggested by Engel.[29] Of 23 patients with acute symptomatology arising from the biliary tract, 18 (78 per cent) showed cardiac standstill of 3 seconds or more after massage of the carotid sinus. Ten of these 18 were examined post-operatively; carotid sinus hypersensitivity had disappeared in seven. Although nine of the 18 had had electrocardiographic abnormalities, six of seven examined post-operatively had insensitive carotid sinuses. This evidence was interpreted as showing a summation of afferent impulses from end organs in the biliary tract which had reached the threshold of reaction of vagal centers in the medulla.

Cerebral Effects

Although Forster et al. found no gross disorder of cortical rhythm during syncope by routine electroencephalographic methods, the majority of cases with circulatory type carotid sinus hypersensitivity showed, on spectrum analysis with the Grass analyzer, a slowing of cortical activity during the period of unconsciousness.[30] By contrast Engel and his associates demonstrated in seven cases of the cardioinhibitory type slow waves, three to six per second, of moderate to high voltage.[31]

Treatment

Pharmacologic treatment of the carotid sinus syndrome has been directed either toward blocking of vagal impulses by atropine or belladonna, or toward establishment of independent ventricular rhythm by ephedrine.[1, 2, 4] Where the last is used, phenobarbital should be added to reduce nervousness.[2] Related drugs such as benzedrine have also been prescribed[32]; in one series modified rest and phenobarbital appeared effective.[8] Resistant cases have been treated by surgical denervation of the carotid sinus [10, 16, 21] and even by x-ray.[7]

Case Reports

Case 1. A 50-year-old physician complained of frequent episodes of unconsciousness ushered in by a feeling of tightness in the chest. Characteristically the attacks came on while the patient dozed in a chair after supper. He would suddenly awaken with discomfort in the upper chest and neck as if his necktie had suddenly been drawn taut. After a moment or two he would lose consciousness. Upon such occasions his wife would observe pallor, snoring respirations, and twitching of the face. Once vomiting and involuntary defecation occurred. Following attacks he would feel quite weak for variable periods of time. Of late he had discovered that he could abort attacks by taking a stiff drink of straight whisky; accordingly, he carried a flask at all times.

Review of the past history disclosed that very infrequent attacks of the sort described had occurred during sleep for many years, but that for four years they had been experienced at least once a week. Once a physician who observed him during an episode at his office told him that he looked very pale, was sweating profusely, and had an unobtainable pulse and blood pressure. Frequent physical examinations, including electrocardiographic studies, had failed to disclose any abnormality.

Except for typhoid as a youngster and gastric ulcer in 1927 the patient had had no serious illnesses.

Physical examination disclosed a slightly obese, pale white male in no distress. The heart was not enlarged; rhythm, regular at 64 per minute; heart sounds of normal quality. Retinal and peripheral arteries appeared normal. Blood pressure was 120 mm. Hg systolic and 75 mm. diastolic, in the supine position, 112 systolic in the sitting, and 102 systolic in the standing position. Routine blood counts were normal, and an electrocardiogram was entirely normal.

Right carotid sinus pressure with the patient lying semi-upright produced a slight sensation of faintness, with twitching of the left face and hand. The seizure resembled petit mal. Marked slowing of the heart resulted. Left carotid sinus pressure produced no symptoms. Bilateral carotid sinus compression, with the use of moderate pressure, caused prompt unconsciousness, snoring, stertorous respirations, and twitching of the left side of the face. A period of asystole lasting 7.2 seconds resulted (figure 1).

The patient was immediately started on ephedrine sulfate .025 gm. and phenobarbital .016 gm. thrice daily. Since the ephedrine made him very nervous, the medication was changed to extract of belladonna .016 gm. thrice daily. Except for one abortive attack, characterized by tingling of the extremities and tightness of the neck, occurring during the interval when medications were changed, there have been no further seizures in 18 months.

Three months after his original visit the patient reported six weekly attacks consisting of sudden painful constriction in the mid-chest radiating down both arms, associated with a strong desire for removal of his false teeth. Although the abrupt onset of pain occurred at rest, the patient had usually been exerting himself severely a few

hours before. Lasting only "a few minutes," the attacks were relieved by lying down. Physical examination and electrocardiogram disclosed no abnormalities of significance. Nitroglycerine, however, was found to provide instant relief, thus confirming the diagnosis of anginal syndrome.

For the past year the patient has been doing very well on modified rest and extract of belladonna, .016 gm. daily, the dose having gradually been reduced over a period of four months. Anginal attacks have been very rare, and syncope has not recurred.

Comment: This first case is reported at considerable length to bring out the following features: characteristic, undiagnosed syncopal attacks had been experienced, though rarely, for many years, with increasing frequency for

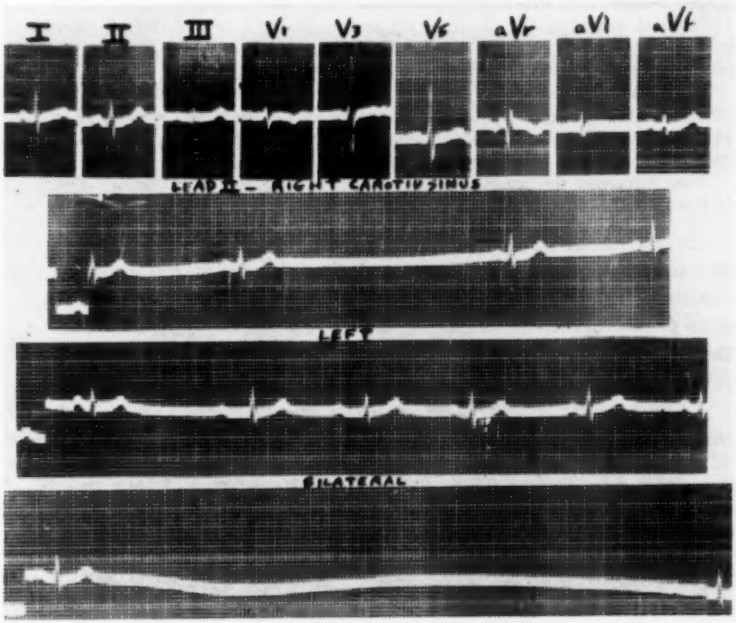

FIG. 1. Electrocardiographic record of Case 1.

four years; they were associated with direct pressure, nodding over a tight collar; they were prevented by alcohol; carotid sinus pressure reproduced the symptoms, and belladonna abolished them. Although objective signs of cardiovascular disease were lacking, the patient subsequently developed typical angina pectoris.

Two mistakes were made in the technic of examination; the patient was supine when carotid sinus pressure was applied, a position tending to diminish a positive response; and bilateral pressure was applied, a maneuver considered dangerous by most authorities.

Case 2. A 50-year-old director of a local Government agency had noticed for one month that sudden turning of the head, especially to the right, caused momentary dizziness and staggering. At times abrupt rising from a chair had the same effect. For three or four months, whenever he walked uphill, particularly in a cold wind, he had had severe substernal pain radiating down both arms, lasting a few minutes, relieved by rest.

Three years before, while on Navy duty, he had suffered a typical myocardial infarction. After discharge from the Navy he secured a job as first aid man in the shipyards. Clambering about construction work caused substernal tightness radiating to the left elbow, relieved by rest. Nitroglycerine, the one time it was tried, produced immediate loss of consciousness. Exchanging an active for a sedentary occupation led to disappearance of untoward symptoms for almost two years, when angina pectoris recurred as described above.

Physical examination was entirely within normal limits. Blood pressure, 120 mm. Hg systolic and 80 mm. diastolic. Except for persistent Q waves in all limb leads the electrocardiogram was normal.

Right carotid sinus pressure with the patient supine caused blinking and twitching of the face; dizziness, according to the patient, had been reproduced. The electrocardiogram showed 34 per cent slowing of the heart rate, from 68 to 45 beats per minute.

Soon after this first visit the patient became a Christian Scientist. Death, probably from another myocardial infarction, ensued three months later.

Comment: Striking in this case was the history of myocardial infarction succeeded by the anginal syndrome and, finally, by another fatal infarction.

Although the incorrect supine position was again used during the application of pressure, the carotid sinus syndrome was demonstrated in that symptoms were reproduced and a 3 + reaction was registered by electrocardiogram.

Case 3. A 52-year-old executive had had for five years recurrent attacks of pulmonary infection tentatively diagnosed on one occasion as tuberculosis. At onset, in 1942, he remained in bed 13 weeks; again, two years later, chronic cough recurred and he spent three months abed. For five ensuing years he had done well, but three weeks before consultation he had again developed a respiratory infection with nonproductive cough. On three or four occasions he had, during a paroxysm of coughing, completely lost consciousness for two or three minutes. There was no history suggestive of cardiovascular disease.

Physical examination was entirely unrevealing; pulse 84; blood pressure 128 mm. Hg systolic and 86 mm. diastolic. Chest roentgenogram showed no recent pulmonary infiltration, though there was an area of fibrosis in the upper left lobe which did not appear active. An electrocardiogram was definitely abnormal, showing definite left axis deviation with the heart in the horizontal position, slurring of the QRS complexes in Leads II, III, and aVf, and a flat T wave in Lead aVl (figure 2).

Right carotid sinus pressure caused momentary dizziness and a drop in heart rate from 94 to 38 beats per minute (60 per cent) (figure 2).

Ephedrine sulfate .025 gm. twice daily gave complete relief from dizziness during coughing spells, but was discontinued after one week. No further cough or fainting has been experienced.

Comment: The predisposing factor of paroxysmal coughing in this case very likely provided strong vagal stimulation. The abnormal electrocardiogram, in addition, suggested arteriosclerotic heart disease.

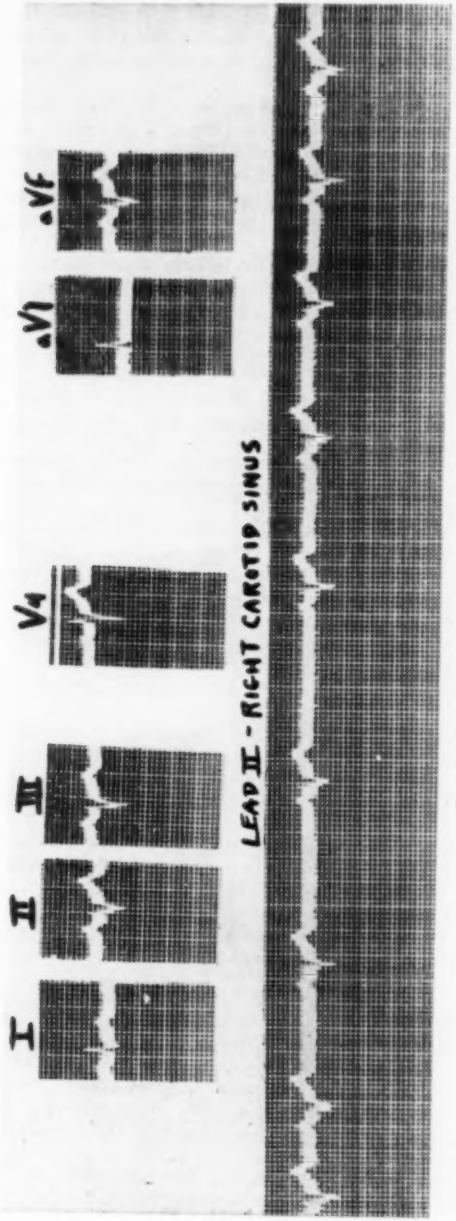

FIG. 2. Electrocardiographic record of Case 3.

Case 4. A 57-year-old merchant complained of listlessness and lack of energy for one year, and bouts of "swimmy-headedness, without loss of consciousness, upon lying down or getting up for the preceding three to four weeks. The cardiac history was entirely negative.

Physical examination was not revealing; pulse, 78; blood pressure 110 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram was within normal limits.

Right carotid sinus pressure produced tingling in all extremities and slight "swimmy-headedness"; pressure on the left caused numbness "all over" and momentary loss of consciousness. The electrocardiogram showed, in the first instance, slowing of the pulse rate from 64 to 42 per minute; in the second, cardiac standstill, except for one complex, for 4.25 seconds.

The patient was given ephedrine sulfate .025 gm. thrice daily, which proved effective in controlling dizziness but caused nervousness and sleeplessness. After one week the drug was replaced by extract of belladonna .016 gm. thrice daily, since which time the patient has remained asymptomatic.

Comment: In this instance no proof of cardiovascular disease was forthcoming. Belladonna afforded relief from symptoms without causing unpleasant side reactions, which led to the discontinuance of ephedrine.

Case 5. A 60-year-old railroad conductor was first seen September 14, 1947 because of a history of aching midchest pain extending down both arms and lasting 5 to 10 minutes occurring two weeks previously. Twelve days later he had a similar attack accompanied by sweating and dyspnea, followed 24 hours later by yet another lasting 15 to 20 minutes. Five years before he had had a skipping of the heart, but at no time had symptoms suggesting heart failure or hypertension been experienced.

Physical examination and fluoroscopy were essentially unrevealing except for a bradycardia of 56 beats per minute, peripheral arteriosclerosis, and slight widening of the aortic shadow. Blood pressure was 150 mm. Hg systolic and 85 mm. diastolic. An electrocardiogram showed no abnormality.

The patient was put on a schedule of modified rest and nitroglycerine for chest pain.

Three weeks later the patient reported having had a number of "giddy spells" brought on by turning around or rising from a chair. Although the sensation was but momentary and not attended by complete loss of consciousness, it had become a source of real concern. Two attacks of chest pain had been immediately controlled by nitroglycerine.

Right carotid sinus pressure caused "burning" of the extremities, extreme giddiness, and momentary loss of consciousness. The electrocardiographic record showed cardiac standstill of 4.2 seconds (figure 3).

Extract of belladonna .016 gm. twice daily was administered with the result that there have been no further recurrences of giddiness. For two months there were no further episodes of angina, but these have tended of late months to become more frequent.

Comment: In this case symptoms of angina pectoris preceded by one month those of the carotid sinus syndrome, which has been well controlled by belladonna.

Case 6. A 78-year-old retired textile worker had for three years been having attacks of faintness brought on by turning around or rising from a chair. Complete loss of consciousness, resulting on at least two occasions in severe falls, usually took place. No aura or residual phenomena had been observed. Except for a bout of "pleurisy" six years before, the past history was unremarkable.

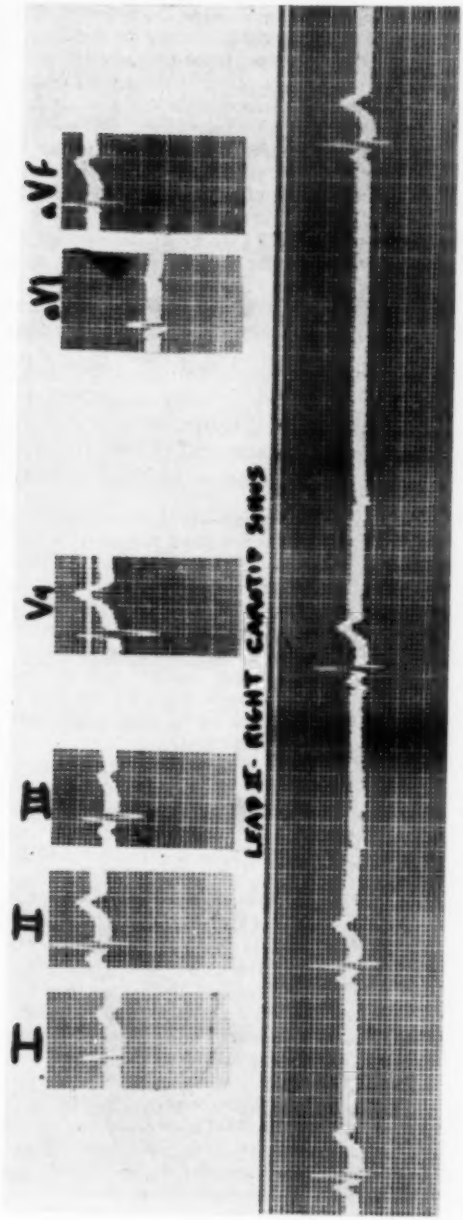

FIG. 3. Electrocardiographic record of Case 5.

Outstanding upon physical examination were these findings: moderate cardiac enlargement with a grade 3 blowing systolic murmur at the apex; cardiac rhythm slightly irregular at a rate of 92 per minute; blood pressure 165 mm. Hg systolic and 100 mm. diastolic; broadening of the light reflex of the retinal arterioles; and moderately sclerotic peripheral arteries. Fluoroscopy showed distinct left ventricular enlargement in the left anterior oblique position without marked increase in cardiothoracic ratio. An electrocardiogram showed prolongation of the PR interval (.22) with an occasional dropped beat, frequent ventricular premature beats, and signs of old anterior myocardial infarction consisting of a Q wave in Lead I, all chest leads, and aV1, and inverted T waves in Leads I and aV1.

Right carotid sinus pressure produced tingling of the extremities and momentary unconsciousness. The electrocardiographic tracing showed cardiac standstill of 4.04 seconds.

Extract of belladonna and phenobarbital have, except for mild "swimmy-headedness" during the first three weeks of therapy, afforded complete relief from syncope.

Comment: In this case there was definite electrocardiographic evidence of old anterior myocardial infarction, possibly diagnosed as "pleurisy" six years before, as well as auriculo-ventricular block probably resulting from arteriosclerotic heart disease. True syncopal attacks reproducible by carotid sinus pressure were prevented by belladonna and phenobarbital.

Case 7. A 72-year-old former salesman who had entered Mecklenburg County Sanatorium in 1931 with a diagnosis of far advanced pulmonary tuberculosis had begun having frequent "dizzy spells" in 1942. After extensive neurological studies another physician found no evidence of an intracranial lesion, but gave him atropine twice daily by hypodermic to relieve post cibal abdominal distention and "overloading of the stomach." Distinct benefit was derived from this therapy; so long as it continued the patient had only a few attacks of mild faintness. In the summer of 1943 he suffered transitory paralysis of the right arm and leg, and left face. Thereafter he did well until three or four months before consultation when he again began having severe dizzy spells, usually occurring when he was on his feet, but not definitely related to change of position. Often these came on at meal time, accompanied by nausea and vomiting of brief duration. Though extremely faint at such times, the patient had never lost consciousness.

Except for his pulmonary tuberculosis, which had involved the entire left lung, and for which he had undergone left phrenicotomy in 1933, the patient's past history was irrelevant. For years the sputum had been negative for acid fast organisms, and the patient had been ambulatory.

Physical examination disclosed a querulous, elderly white male in no distress. Blood pressure, 175 mm. Hg systolic and 95 mm. diastolic. Pulse, regular at 76 per minute. The heart was displaced well to the left; the pulmonic second sound was louder than the aortic. The peripheral arteries were moderately sclerotic. Chest x-ray showed elevation of the left diaphragm, displacement of the heart to the left, and wide areas of density throughout the left lung field, where a questionable cavity was made out anteriorly just lateral to the heart shadow. An electrocardiogram showed prolongation of the PR interval (.22 sec.) and abnormal T waves in Leads I and aV1 (figure 4).

Pressure on the right carotid sinus with the patient sitting on the edge of his bed caused disappearance of the radial pulse and immediate loss of consciousness, with snoring respirations and clonic twitching of all extremities. Repeated 15 minutes later with the patient connected to an electrocardiograph, the maneuver again caused syncope, the electrocardiographic tracing showing asystole of 6.56 seconds (figure 4).

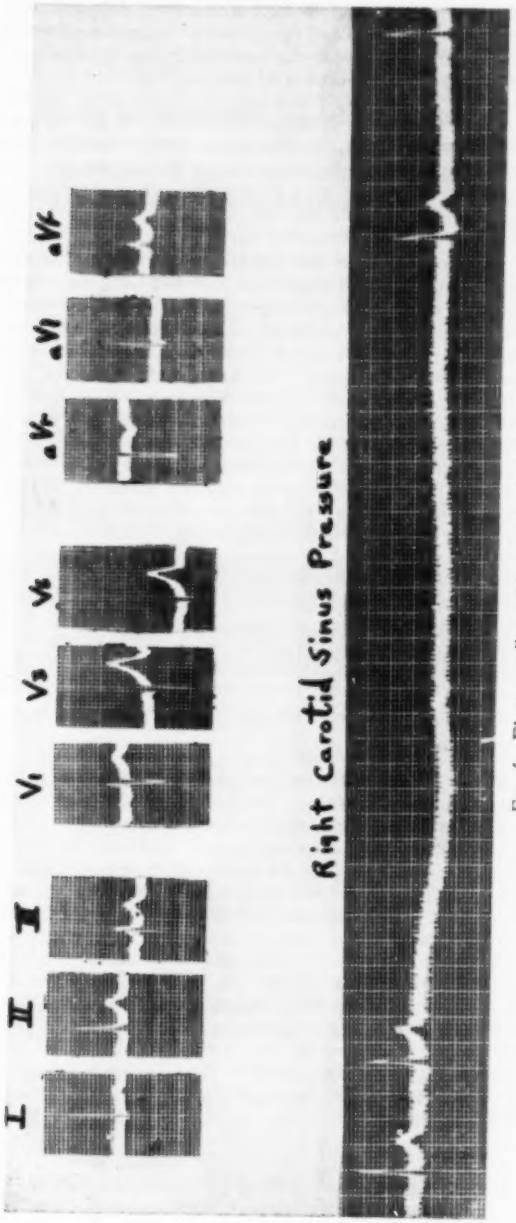

FIG. 4. Electrocardiographic record of Case 7.

Atropine sulfate grains 1/100 thrice daily was started, followed after 10 days by extract of belladonna .016 gm. thrice daily. After a month free from symptoms the patient discontinued the drugs. During the succeeding month no severe attacks have occurred, though he had reported several mild ones.

Comment: Transitory hemiplegia, elevated blood pressure, and an abnormal electrocardiogram attest, in this case, cardiovascular disease. Episodes of syncope, while not complete nor related to specific actions on the part of the patient, were reproducible by carotid sinus pressure and abolished by atropine and belladonna.

Case 8. A 43-year-old salesman had had six or seven attacks of severe faintness during the preceding six months. Though one occurred while he was driving a car, the others all took place while he was sitting in a chair. First he would note a sour taste in the mouth, then blurring of vision or severe diplopia followed by fainting. In addition, he had had three severe attacks of squeezing midchest pain lasting about five minutes accompanied by severe dyspnea, once while on a long drive, once right after a meal, and once while walking rapidly. There was no history of hypertension.

Physical examination showed a rather obese white male in no distress. Pulse, 84 per minute; blood pressure, 120 mm. Hg systolic and 80 mm. diastolic. There were no significant abnormal findings. An electrocardiogram was within normal limits.

Right carotid sinus pressure caused only moderate dizziness, but pressure on the left caused the mouth to fill with sour fluid, pronounced blurring of vision, and extreme giddiness. To the observer the patient seemed to stare blankly, with wavering eyes. For one minute he did not respond to questioning. The electrocardiogram showed one ventricular complex and three auricular complexes in a period of 5.16 seconds.

A regimen of modified rest was imposed, and extract of belladonna .016 gm. thrice daily was prescribed. Thus far there have been no further attacks of dizziness.

Comment: A comparatively young man gave a history strongly suggesting anginal syndrome, though objective signs of cardiovascular disease were lacking. Strong aura preceded syncopal attacks and were evoked by carotid sinus pressure.

Case 9. A 47-year-old executive had suffered from attacks of syncope occurring every two months for about 18 months. The first attack came on as the patient was choking on a piece of bread; complete loss of consciousness ensued. All but one of his subsequent episodes occurred right after meals; once he gashed his forehead as he fell to the floor while paying the cashier for his dinner. The last attack came on while he was at stool; shortly beforehand he had choked on some cough syrup. No aura or residual phenomena had been observed. There was no history of cardiovascular disease.

Physical examination was entirely within normal limits except for slight obesity. Pulse, 84 per minute; blood pressure 120 mm. Hg systolic and 80 mm. diastolic.

Right carotid sinus pressure resulted in immediate loss of consciousness, though pressure was maintained for only seven seconds. Slight clonic twitching of all extremities was noted, and for 15 seconds after awakening the patient was disoriented. The electrocardiogram showed cardiac standstill for 5.4 seconds (figure 5).

Extract of belladonna .016 gm. twice daily was prescribed. No further attacks have been reported.

Comment: Exceptionally severe syncopal attacks followed vagal stimulation by choking or swallowing; several bouts followed hearty meals. There were no symptoms suggesting cardiovascular disease.

Case 10. A 66-year-old housewife had had her first "sinking spell" one year ago, but during the preceding three weeks these had become an almost daily occurrence. Lying down or "raising up" quickly caused something to "hit her in the chest and travel out the top of her head," an "awful taste" would appear in the mouth, and extreme dizziness lasting several moments would supervene. Her husband stated that the blood would leave her face and she would develop the "blind staggers"; once he took her pulse, finding it extremely slow. Except for "skipping of the heart" following influenza in 1921 the patient had had no cardiovascular symptoms.

Physical examination revealed the following relevant features: blood pressure 158 mm. Hg systolic and 70 mm. diastolic; pulse regular at a rate of 64 per minute; heart slightly enlarged to percussion, apical second sound split; grade 1 apical systolic murmur; broadening of the light reflex of the retinal arterioles; and mild sclerosis of peripheral arteries. Fluoroscopy showed slight enlargement of the left ventricle in the left anterior oblique position. An electrocardiogram showed first degree auriculoventricular block, with a PR interval of .22 second.

FIG. 5. Electrocardiographic record of Case 9.

Right carotid sinus pressure caused blinking, deep respirations, and twitching of the right hand. The patient later stated that she had grown extremely dizzy and had momentarily lost consciousness during the procedure. Pressure on the left caused giddiness, not so pronounced as the first. The electrocardiogram showed, during right carotid sinus pressure, no ventricular impulse for 2.8 seconds; repeated five minutes later the maneuver caused complete sinus arrest with slowing of the ventricular rate from 84 to 34 per minute (60 per cent).

A trial of belladonna was begun. Upon her first return visit two weeks later the patient said she had had no giddiness except upon getting out of bed in the morning.

Comment: Left ventricular enlargement and a prolonged PR interval were objective signs of heart disease in this, the only female in the series. Carotid sinus pressure caused, in one trial, sinus arrest.

Case 11. A 55-year-old farmer in May, 1947 suffered what he called a "light stroke," characterized by sudden "drawing" pain in the throat, dizziness, and severe headache. He did not lose consciousness, nor were difficulties of speech, vision, gait, or sphincter control noted. A doctor who saw him the same day told him his blood pressure was "285." Frequent headaches and occasional giddy sensations had bothered him ever since. Two years before consultation he had, after reaching up to jerk a lever on his tractor, suffered a "tearing" pain in the center of the chest which lasted

one-half hour, leaving him quite weak. Since then lifting or strenuous effort had caused recurrence of chest pain, though ordinary exertion had no ill effect.

Physical examination disclosed an enormously obese white man of middle age, 5 feet 9.5 inches tall, weighing 247 pounds. Blood pressure, right arm, 175 mm. Hg systolic and 115 mm. diastolic; left arm, 145 systolic and 95 diastolic. Pulse, regular at 84 per minute. The retinal arterioles were narrow, and compressed the venules where crossing them. The heart was slightly enlarged to percussion; the aortic second sound was ringing and louder than the pulmonic, and there was a short, blowing, apical systolic murmur. The liver edge could be felt 2 cm. below the right costal margin on deep inspiration. There were no other relevant findings. Fluoroscopy showed slight left ventricular enlargement in the left anterior oblique position. An electrocardiogram showed a horizontal heart but no striking abnormality.

The patient was given a reducing diet, phenobarbital, and a regimen of modified rest.

During the ensuing seven weeks the patient had a number of giddy sensations, not accompanied by loss of consciousness and only occasionally related to change of position, which caused him genuine concern. He would either sit down abruptly or clutch for support until this momentary sensation had passed. At times, too, he had occasional "tearing" pain across the upper abdomen, unrelated to meals or exertion, which lasted from several minutes to several days.

At this visit carotid sinus pressure was tried. So long as pressure was maintained over the right sinus no pulse was felt at the wrist. When repeated after the patient had been connected to an electrocardiograph, pressure caused giddiness and blank staring, said later by the patient to mimic his attacks very closely except for the longer duration of the latter. The tracing showed ventricular standstill for 5 seconds, though one questionable auricular beat came through.

Extract of belladonna was begun in the usual dosage, and phenobarbital was continued.

Comment: Arterial hypertension, with an episode of possible hypertensive encephalopathy, and questionable angina pectoris were, besides obesity, the factors to be reckoned with before attention was drawn to the giddy sensations. Right carotid sinus pressure reproduced these last and had a strong effect on heart rate as proved by a concomitant electrocardiogram.

Summary and Conclusions

The demonstration of hyperactive carotid sinus reflex solves many puzzling cases of syncope; 11 such cases have been presented. Although a review of the literature would indicate that precipitating factors are reported in only a minority, in eight of the present series these were noted: sudden change of position (Cases 2, 4, 5, 6, and 10), strong vagal stimuli (Cases 3 and 9), and external pressure over the carotid sinus (Case 1). Proof that carotid sinus irritability has caused syncopal attacks is afforded by mechanical pressure alternatively over the carotid sinus areas which both reproduces the symptoms and shows definite effect on heart rate as recorded on a simultaneous electrocardiogram. Classification of responses in the present series shows six cases with 4 + and five cases with 3 + responses.

A review of the literature has shown that the chief factors conditioning the circulatory response to carotid sinus pressure appear to be age, sex, and

the presence of heart disease, especially arteriosclerotic. Of the 11 cases of carotid sinus syndrome herein reported, 10 were males; two were in the eighth decade, two in the seventh, five in the sixth, and two in the fifth. In nine cases there was evidence of heart disease. Four (Cases 1, 2, 5, and 8) gave histories diagnostic of the anginal syndrome, one of which (Case 2) had suffered one myocardial infarction and subsequently died, in all probability, of a second. Four others had definitely abnormal electrocardiograms (Cases 3, 6, 7, and 10); two of these (6 and 7) also had arterial hypertension. In one instance (Case 11) hypertension alone was demonstrable. Peripheral arteriosclerosis of significant degree was observed in only three patients (Cases 6, 7, and 10). This report of 11 successive cases of carotid sinus syndrome, therefore, lends further weight to the current thesis asserting the presence of underlying heart disease in carotid sinus hypersensitivity.

All of the patients in the present series responded satisfactorily to therapy with extract of belladonna, with or without phenobarbital, in that no further attacks of fainting occurred. Since carefully controlled study was impossible for office patients, and since electrocardiographic records during carotid sinus pressure were not repeated after medication had been begun, these results cannot be claimed as specific.

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NODAL TACHYCARDIA FOLLOWING DIGITALIS OVERDOSAGE (STOPPED BY CAROTID SINUS PRESSURE): REPORT OF TWO CASES*

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ONE of the manifestations of digitalis overdosage may be the sudden occurrence of a regular tachycardia. Ventricular tachycardia has been described most commonly.[1, 2, 3, 4, 5, 6, 7, 8] More rarely auricular tachycardia has been observed.[6, 9, 10] Three cases of auricular flutter following toxic doses of digitalis have been reported,[11, 12] whereas there has been only one reported case of nodal tachycardia.[13]

This paper presents two additional cases of nodal tachycardia following digitalis therapy. Moreover, these patients demonstrated an unusual clinical course and an uncommon series of electrocardiograms that are deemed worth reporting.

Without regard to etiology, in a series of 94,000 electrocardiograms taken at the Boston City Hospital there were approximately 75 other cases of nodal tachycardia and about 38 cases that were questionable. Not one of these demonstrated the sequence of events to be described.

CASE REPORTS

Case 1. A 65 year old American Negro entered the Boston City Hospital on September 17, 1941, with a chief complaint of shortness of breath lasting two years.

Two years before entry the patient began to note dyspnea on exertion, orthopnea and occasional ankle edema. These symptoms progressed. In May, 1941, he entered another hospital because of severe shortness of breath of five days' duration. He remained there overnight and electrocardiograms at that time showed slight changes, which were thought to be consistent with a recent myocardial infarction. The rhythm of the heart was regular (table 1 and figure 1). He was advised to appear for follow-up at their out-patient department.

He went there one month later with symptoms and signs of moderate cardiac failure and the cardiac rhythm was again found to be regular. He was told to take 22.5 grains of digitalis over a six day period. When he returned at the end of six days the rhythm was irregular and the heart rate was 60 per minute. One and one-half grains of digitalis daily was continued. In late August, 1941, he again returned, complaining of anginal pain. He was advised to continue the digitalis and, in addition, theocalcin and restriction of fluid intake were prescribed.

On September 14 he was found in severe cardiac failure. He denied taking digitalis, but exhibited some pills, each containing 0.5 grain of digitalis, of which he stated he had taken only two. On examination, the heart rhythm was grossly irregular and the rate was 120 per minute. He was given six grains of digitalis intravenously and 12 grains to take by mouth in the next eight hours. The next day the

* Received for publication March 25, 1948.
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Aided by a grant from the Charlton Fund.

TABLE I

Summary of Electrocardiograms of Case 1

Date	Rhythm	Rate	P–R Interval	P Waves	Q–S Interval	QRS Complexes	T Waves	Other Findings
5/14/41	Normal sinus	83	0.15	P_1, P_2, P_3 notched	0.06	Low (6 mm.) voltage; slurred	Slightly inverted T_1. Low diphasic T_3 and T_4	Tendency to left axis. One auricular and one ventricular premature beat
5/15 figure 1	Same	80	0.13	Same. Inverted P_4	0.06	Same	Definitely inverted T_1 and T_4. T_3 and T_2 same	Left axis
9/18 figure 2	Nodal tachy-cardia	158	—	F waves in L_1, L_4 and 3R	0.08	Low (5 mm.) voltage. Deep S_1	T_1, T_2, T_3 low. T_4 inverted	? marked right axis ? increase in left axis
9/19 figure 3. After carotid sinus pr.	Auricular fibrillation	70	—	—	0.07	Low (5 mm.) voltage	T_1, T_2, T_4 inverted, T_3 up	Left axis
12/23 figure 4	Auricular fibrillation	120	—	—	0.08	Same	T_1, T_2 inverted. T_3, T_4 up	Same. Ectopic beats all leads. (? origin)
6/18/42	Normal sinus	107	0.15	P_1, P_2, P_3 notched	0.08	Low (3 mm.) voltage	T_1, T_3, T_2 inverted T_4 up	Normal axis

rhythm was still irregular, but the rate was 60 per minute. He was given mercupurin intramuscularly, and ammonium chloride and three grains of digitalis by mouth. This brought the known total dosage of digitalis to 21 grains. On the third and fourth days digitalis was omitted. When seen on the fourth day his heart rate was 140 per minute and the rhythm was regular. He was sent into the Boston City Hospital.

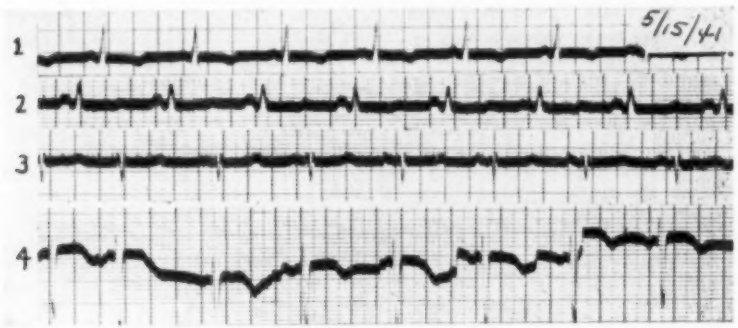

FIG. 1. Case 1.

Examination showed a drowsy patient in no acute respiratory distress. There was slight engorgement of the neck veins. Signs of fluid were evident at the right base. The heart was slightly enlarged to the left. The rhythm was regular and the rate was 140 per minute. There was a presystolic gallop. Pitting edema, diminishing up to the umbilicus, was noted. The blood pressure was 160 mm. Hg systolic and 130 mm. diastolic. His weight was about 140 lbs. Temperature was 98.6°, and respirations were 22 per minute.

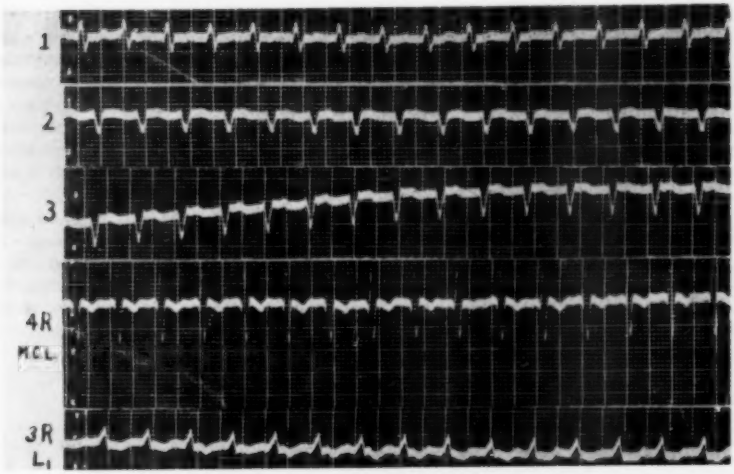

FIG. 2. Case 1, September 18, 1941.

Urine showed a specific gravity ranging from 1.012 to 1.018, a very slight trace to a slight trace of albumin and the sediment was negative. Blood counts were normal. The Hinton reaction was negative. The non-protein nitrogen content of the blood was 53 mg. per cent on September 17 and 73 mg. per cent on September 21. Thereafter it was normal. The total serum protein was 5.3 gm. per cent. A chest plate showed the heart enlarged transversely.

An electrocardiogram was obtained shortly after admission (table 1 and figure 2). Because of the tachycardia, carotid sinus pressure was performed the day after entry.

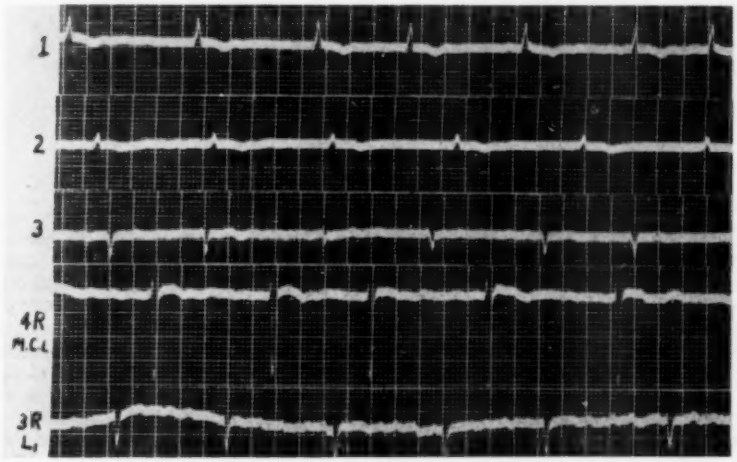

FIG. 3. Case 1, September 19, 1941.

Pressure on the right carotid sinus had no effect, but pressure over the left resulted immediately in a marked drop in rate and in the onset of an irregular rhythm which persisted. This was found to be auricular fibrillation by an electrocardiogram taken the next day (table 1 and figure 3). Up to this time the patient had had no medication in the hospital except ammonium chloride. He was further treated by means of two chest taps, limited fluids, mercupurin, and ammonium chloride. He improved markedly and on the tenth day 1.5 grains of digitalis were ordered. Because his heart rate dropped to 60 on the twenty-second day, he was discharged on this dosage of digitalis every other day.

The patient was followed in the out-patient department. He was careless about following the prescribed digitalis dosage and was seen again in cardiac failure. An electrocardiogram showed, in addition to fibrillation, ectopic ventricular beats in all leads (table 1 and figure 4). At a later check-up there was evidence of digitalis toxicity but when seen subsequently he was fairly well. Auricular fibrillation was found at every examination.

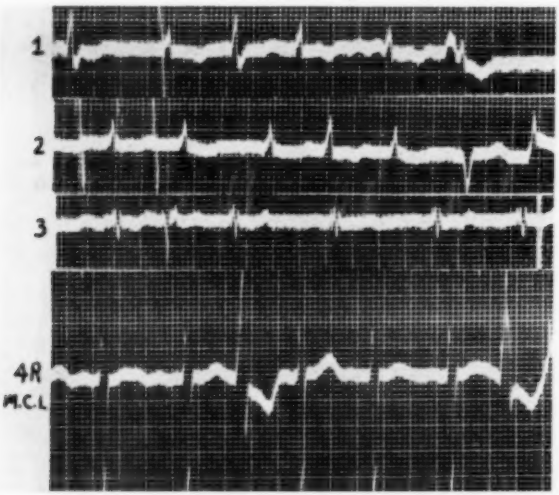

FIG. 4. Case 1, December 23, 1941.

On June 17, 1942 he was admitted in coma. There was clinical evidence of a cerebral vascular accident. The heart was considerably enlarged. The rhythm was now regular except for some extrasystoles. The blood pressure was 90/60. There were signs of fluid in the right chest and pitting edema of both legs. An electrocardiogram showed a normal sinus rhythm (table 1). He remained in coma and died on the third hospital day. An autopsy was not obtained.

Case 2. An 80 year old Albanian entered the Boston City Hospital on October 20, 1941, with a chief complaint of abdominal pain for one day.

The patient had been in good health until 10 months before entry, when he developed ankle edema and had nocturia three to four times nightly. He remained up and about until two months before admission, when he felt generally poorly and developed dyspnea on exertion. A doctor found little dyspnea, but noted that the

cardiac rhythm was irregular and the systolic blood pressure was 190 mm. of mercury. He prescribed 30 grains of digitalis to be taken in two days. At the end of this time the patient's heart rhythm became regular. Digitalis in doses of 1.5 grains was continued daily, but the medication improved the patient so much that he discontinued it after two weeks. He felt well until the day before admission when he complained of right lower quadrant pain and mild epigastric distress. The same doctor found the patient dyspneic and complaining that he was unable to urinate; and he therefore sent him to the Boston City Hospital.

Examination showed a cyanotic and semi-stuporous patient. He had received ⅙ grain of morphine sulfate on the accident floor. His skin was moist and cold, the neck veins were distended, and he was breathing shallowly. Signs of fluid were present at the left base and many moist râles were heard at the right base. The apex impulse was felt at the mid-axillary line and the cardiac rhythm was grossly irregular. The liver was felt four fingers'-breadth below the costal margin. A right inguinal hernia was easily reduced. Edema was marked in the scrotum, forearms and legs. The blood pressure was 210/110. His weight was about 125 lbs. Temperature was 98.6°, apex rate was 120, pulse rate was 96 and respirations were 30 per minute.

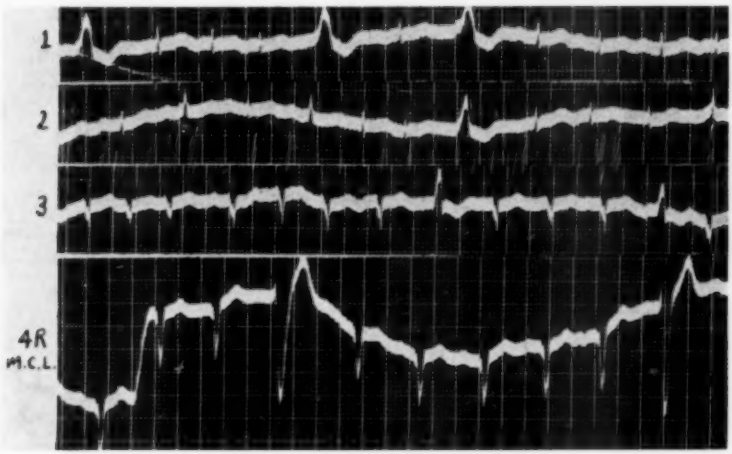

FIG. 5. Case 2, October 20, 1941.

One urine specimen showed a specific gravity of 1.016, the slightest possible trace of albumin and a negative sediment. Blood examinations revealed normal values. The non-protein nitrogen of the blood was 27 to 32 mg. per cent. The Hinton reaction was negative. The venous pressure in each arm was 132 to 145 mm. of water, while the circulation time from arm to tongue with decholin was 22 to 25 seconds. The blood sedimentation rate (Westergren), in mm. per hour, was 25 on October 20, 49 on November 7, and 67 on November 14. This latter was associated with a terminal temperature rise. A chest plate revealed transverse enlargement of the heart with bilateral congestive changes in the lungs.

The patient was given 22.5 grains of digitalis in 24 hours and thereafter 1.5 grains daily. An electrocardiogram taken after he had received 7.5 grains of the drug showed auricular fibrillation (table 2 and figure 5). Fluids were limited and

his left chest was tapped on the second hospital day. At the end of 48 hours (after 24 grains of digitalis), his pulse was noted to be rapid and regular and an electrocardiogram showed a tachycardia with a rate of 160 per minute (table 2). The next day the rate had dropped to 145 per minute. The rhythm was perfectly regular. Electrocardiograms were taken before and after carotid sinus pressure (table 2 and figure 6). Right carotid sinus pressure resulted in the onset of auricular fibrillation with a rate of 70 per minute. Within 20 minutes the rate was back to 145 per minute and the rhythm became regular. On three occasions from the fourth to the seventh hospital days the heart rhythm was changed from a regular tachycardia to a grossly irregular rhythm by pressure over the right carotid sinus. On each occasion after 20 to 30 minutes, the rhythm reverted to a regular tachycardia.

TABLE II

Summary of Electrocardiograms of Case 2

Date	Rhythm	Rate	P–R Interval	P Waves	Q–S Interval	QRS Complexes	T Waves	Other Findings
10/20/41 figure 5	Auricular fibrillation	120	—	—	0.07	Absent R_4 (M.C.L.). Low (4 mm.) voltage. Notching QRS_2 and QRS_4	T_1, T_2, T_3, T_4 up	Left axis; ventricular premature beats all leads
10/22 After gr. xxiv of digitalis	Nodal tachycardia	160	—	Fibrillation waves in 3R	0.09–0.10	R_4 present (apex). Voltage to 10 mm. Slurring QRS_1, QRS_2, QRS_3	T_1 low with low origin. T_2, T_3 up. T_4 diphasic	Axis shifted more to left
10/23 figure 6, before carotid sinus pr.	Same	145	—	Same	Same	Same	Same	Same
Figure 6, after carotid sinus pr.	Auricular fibrillation	90	—	—	0.06	R_4 present (apex). Low (6 mm.) voltage. Slurring all leads	T_1 low. T_2 and T_4 diphasic. T_3 inverted	Less marked left axis. Premature nodal (?) beats L_1
10/25	Same as 10/22	140	Remainder same as 10/22 throughout					
10/28 figure 7	Normal sinus	80	0.16–0.24	P_3 inverted	0.08	R_4 absent (apex). Slurring. Voltage to 7 mm.	T_1, T_2 diphasic. T_3 inverted. T_4 up	Left axis
10/31	Same as 10/28 throughout							
11/7	Same as 10/28 throughout							

On the seventh hospital day a pericardial or pleuro-pericardial rub was heard. The patient did not complain of any pain and looked well. His blood pressure was found to be 115/75. The next day it was 140/80 and it remained at this level. There was no electrocardiographic evidence of myocardial infarction. On the ninth hospital day the rate was noted to be 80 and the rhythm regular. An electrocardiogram showed a normal sinus rhythm (table 2 and figure 7). The patient seemed to be doing well. Râles, however, persisted at both bases. Toward the end of the fourth hospital week he became weaker. His temperature, pulse and respiratory rates rose and he died of pneumonia. The cardiac rhythm remained regular to the end. Autopsy permission was not obtained.

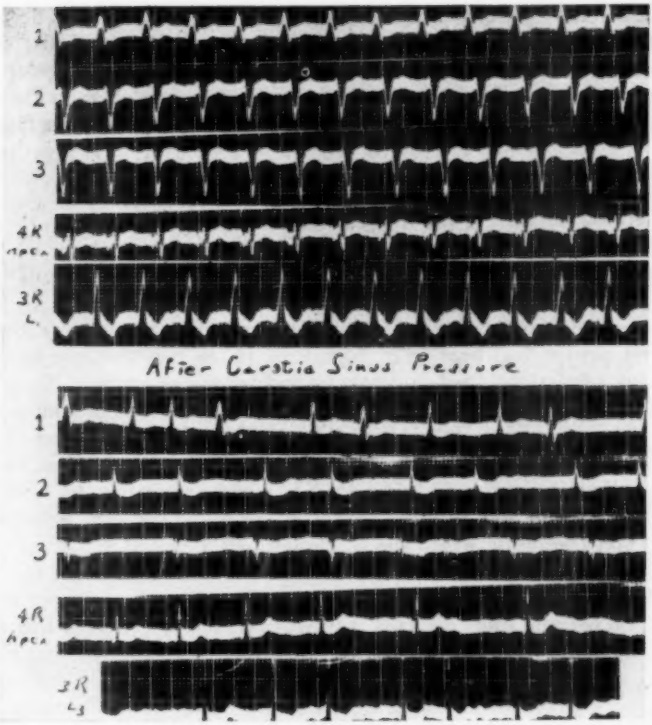

FIG. 6. Case 2, October 23, 1941.

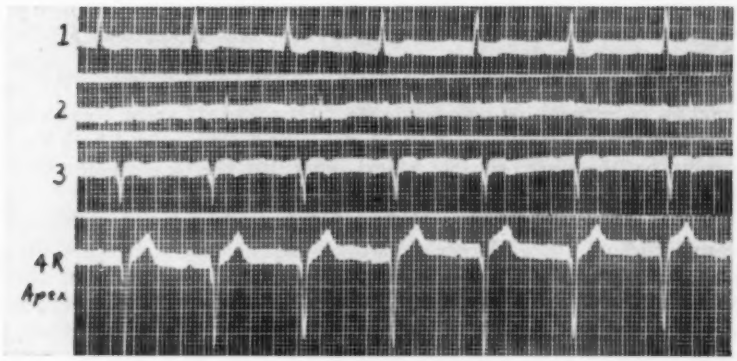

FIG. 7. Case 2, October 28, 1941.

In summary, these two cases concern two elderly men with decompensated hypertensive and arteriosclerotic heart disease and auricular fibrillation. When placed on digitalis, they both developed unusual regular tachycardias. The application of carotid sinus pressure resulted in the disappearance of the tachycardias and the reappearance of auricular fibrillation.

Discussion

Attention is called to the rôle of digitalis in the production of the tachycardias described because of the distinct temporal relationships. The first patient developed a rapid regular rhythm within 48 hours after digitalization. Tachycardia was noted in the second patient within 24 hours.

The evidence indicates that both patients received an excess of the drug. The first patient had been fully digitalized up to two and one-half weeks before his admission. Subsequently he had taken one grain of digitalis and then prior to entry he received 21 grains of digitalis over a course of two days. The second patient had been fully digitalized up to six weeks prior to hospitalization. After admission he received 22.5 grains more in 24 hours.

The digitalis in use was U.S.P. XI, which, according to Edmunds,[14] Gold,[15] and Bland and White,[16] was from 25 to 50 per cent stronger than the old preparation on which the Eggleston and Wyckoff [17] method of digitalization is based. If we use this method and assume that the old dosage should be reduced 30 per cent, we find that Case 1 received 16 per cent and Case 2, 66 per cent more digitalis than was necessary. Because this method is only approximate, Robinson et al.[18] discarded it and stated that the total average dose in an adult who had not received digitalis for 10 days is about 22.5 grains in 36 to 48 hours. This would be about 16.5 grains by our calculations for U.S.P. XI digitalis. Both patients received more than this amount and the second patient was digitalized more rapidly than recommended.

There is also evidence to indicate that these patients had a relative as well as an absolute excess of drug. Cases have been reported by Gilchrist [1] and others [2, 3, 4] in which tachycardias have appeared after small doses of digitalis. Marvin [2] has also noted that under such circumstances the usual symptoms of intoxication may be absent. He stated, "Careful consideration of the doses and the circumstances in which they were used, leaves the impression that there are probably factors other than the total amount of digitalis which may be responsible for the mechanism under discussion."

One of the most important of these factors is the amount of damage to the myocardium.[1, 2, 19] Garrey's [20] work suggests that toxic rhythms are apt to occur in enlarged hearts. Resnik [21] noted transient auricular fibrillation after digitalis in patients with advanced myocardial failure. The toxic dose of digitalis is large for a patient with a fairly good myocardium, but small for patients with severely diseased hearts.

Other factors such as previous digitalization, especially when diuretics

are used,[22] also influence relative toxicity. These factors may have been operating in the two cases discussed here. We lack sufficient data, however, to prove it.

The diagnosis of the type of tachycardia in these cases hinges mainly on the electrocardiograms and the effect of carotid sinus pressure on the rapid rhythms.

Briefly, the rhythm was first that of auricular fibrillation. Digitalis administration resulted in the onset of a rapid regular rhythm, which was converted to auricular fibrillation by carotid sinus pressure.

Two rapid regular rhythms which can be ruled out are auricular tachycardia and auricular flutter. Although occasionally these rhythms may follow digitalis overdosage in patients with normal sinus rhythms, in the fibrillating patient the only effect that digitalis has on the auricle is to speed the circus rate.[23, 24] Moreover, if these rhythms did occur there is no evidence that carotid sinus pressure can convert an auricular tachycardia to fibrillation, although it may rarely do so in the case of flutter.[11] Finally the electrocardiograms show no evidence of auricular tachycardia or auricular flutter.

The explanation for the course of events in these cases is a tachycardia with the impulse originating outside of the auricle. Under these circumstances the auricle continued fibrillating. It is then easy to see why carotid sinus pressure, which abolished the tachycardia, should result in the reappearance of fibrillation. This impulse can be in either the ventricle or the A–V node. Schwensen [3] and also Felberbaum [5] stated that in an established case of auricular fibrillation a tachycardia must be ventricular in type. Marvin,[2] however, has pointed out that the ventricular complex could originate in the junctional tissue. Katz [25] further noted that in auricular fibrillation with complete heart block, the narrow QRS suggests that the origin of the ventricular beat is in the A–V node. Luten [6] recorded two cases of A–V dissociation where the ventricular complexes were supraventricular in type. Thus either nodal or ventricular tachycardia would fit this picture.

Further consideration of the electrocardiograms shows that we are dealing with nodal rather than ventricular tachycardia. In the first place the QRS complexes are supraventricular in type.[25] The width of the QRS is well under 0.12. Any abnormality of the QRS complex is accounted for by the fact that the rapid rate of an already damaged heart interferes with ventricular conduction.

Also in favor of nodal tachycardia is the regularity of the rhythm. The variation in the P–R interval was less than 0.01 second usually and only occasionally up to 0.02 second. Strong and Levine [26] have pointed out that the average variation of the P–R interval in ventricular tachycardia was usually 10 times these figures, although it might be quite regular at one or more periods.

According to Katz [25] the continuous tachycardia noted in these cases supports the idea of a supraventricular type. In ventricular tachycardia there are runs, interspersed with sinus beats. The tachycardia in case 2 lasted at least five days. Also the fact that all beats of the tachycardia derive from one focus suggests a supraventricular tachycardia.[28]

The decision for nodal tachycardia finally rests on the effect of carotid sinus pressure. The effect of vagal stimulation on the ventricle is believed to be indirect, because, if the A–V bundle is severed, vagal stimulation is without effect on the ventricular rate.[23] Clinically Strong and Munroe [27] found that mecholyl and prostigmine, carotid sinus and eyeball pressure had no effect on ventricular tachycardia. Others [1, 7, 28] confirmed some of these negative results. On the other hand, evidence both physiological and clinical can be found everywhere to indicate that we would expect a supraventricular tachycardia to be affected by carotid sinus pressure in such a manner as noted.

A review of some of the cases of so-called ventricular tachycardia following digitalis that appear in the literature brings up the question of whether they might not be better classified for various reasons as nodal in origin.[2, 4, 5, 7, 8, 29] Many so-called auricular tachycardias, where the P waves are not evident, might well be nodal tachycardias. Nodal rhythms are probably more common than generally believed. On some occasions digitalis may be the etiological factor.

Summary and Conclusions

1. Two patients with impaired myocardiums and auricular fibrillation received too much digitalis, both relatively and absolutely. Both developed the unusual rhythm of nodal tachycardia while the auricles continued to fibrillate. Carotid sinus pressure stopped the tachycardia and resulted in the reappearance of fibrillation.

2. Nodal tachycardia due to digitalis is probably more common than believed. Many of the other 75 cases of nodal tachycardias in the Boston City Hospital series followed digitalis administration.

3. Small doses of digitalis can produce specific toxic effects especially in a diseased myocardium.

4. The diagnosis of the tachycardias on the basis of the electrocardiograms and the effect of carotid sinus pressure is discussed.

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CASE REPORTS

CASE OF TETANUS TREATED WITH ANTITOXIN AND D-TUBOCURARINE *

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Patients with tetanus are being treated more frequently with curare and curare-like drugs. Both optimistic and pessimistic reports have appeared in the literature.[1, 2, 3, 4, 5, 6] In the following case some of the complications and dangers of this type of treatment are exemplified.

Case Report

A 70 year old white male was admitted to Duke Hospital stating that he had been in good health until about 10 days previously, when he had developed a dull suboccipital headache with some stiffness of the neck. Within the next three days he began to have difficulty chewing and swallowing due to tightness of his jaws and throat. The stiffness became more generalized, and about a week after the onset it became difficult for him to walk because of stiffness of his legs. Roentgen-rays of skull and cervical spine were taken in another hospital and found to be normal. The patient had no fever during his illness. On admission no history of trauma was obtained. Later during his hospital stay, the patient remembered sticking a sandspur into his finger approximately one week before symptoms began. He had received no therapy at time of admission. Past history was non-contributory.

Physical examination on admission revealed temperature 36.8° C., pulse 84, respirations 24, blood pressure 140/80. In general, he was well preserved and mentally alert but complained of aching and stiffness of his neck and back. No skin lesions were noted. The pupils were equal and reacted to light and on accommodation. It was impossible to open the mouth more than a third of normal because of spasm of the muscles about the jaw. The neck and entire spine were stiff and muscle spasm was very marked. Examination of the heart and lungs showed no abnormalities. Abdominal examination revealed only muscle spasm without tenderness. Rectal examination was normal. The neurological examination was normal except for hyperactive reflexes. Laboratory studies revealed sedimentation rate 2 mm./hr., hemoglobin 14 gm., white blood cells 8,000, and urine clear with a specific gravity of 1.030. Lumbar puncture revealed an initial pressure of 120 mm. water, clear fluid, negative Pandy, mastic, and Wassermann tests. Microscopic examination revealed two lymphocytes to a high power field.

A diagnosis of tetanus was made on admission. Skin test to horse serum was positive and antitoxin was not given because of danger of reaction and the patient's mild symptoms. After 12 hours the patient began having periodic spasms with marked trismus and it became evident that tetanus antitoxin must be administered. Desensitization to tetanus antitoxin was carried out by starting with a 1:10,000

* Received for publication August 4, 1949.
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dilution and gradually increasing the dose and strength with an injection every 15 minutes until 1 c.c. of 1:1 dilution was given. This was followed in 15 minutes by 100,000 units of tetanus antitoxin subcutaneously in the forearm. The next day skin test was repeated and found to be negative. The patient was given 100,000 more units subcutaneously and 100,000 units in 1000 c.c. of 5 per cent dextrose intravenously.

When calcium gluconate and sedation with chloral hydrate failed to prevent tonic convulsions, it was decided to treat the patient with d-tubocurarine. To establish his tolerance to the drug, the first dose was given intravenously. After 60 units there was marked reaction with salivation, laryngeal obstruction, and onset of cyanosis, with mild convulsions. A laryngoscope was quickly passed through the larynx, but this was possible only after cyanosis had been present three or four minutes and the patient was beginning to relax. The vocal cords were noted to be in spasm at the time laryngoscopy was first attempted. After the patient had received oxygen he recovered without any neurological residual, and sensorium was clear. There was rather marked relief of his spasms and the abdominal muscles became much softer. D-tubocurarine was started in a dosage of 30 units intramuscularly every three hours at this time. This dose proved to be too small to maintain relaxation and 40 units were given which seemed to be satisfactory. With the relaxation the patient became unable to void because he could not contract his abdominal muscles; therefore, it became necessary to insert an indwelling catheter. Approximately 30 minutes after receiving the second dose of 40 units of curare, the patient suddenly had onset of salivation, gagging, and cyanosis resembling that seen the previous day after intravenous injection. Since no laryngoscope was available at the time, emergency tracheotomy was performed. The patient also received prostigmine sulfate 1 c.c. intravenously and oxygen directly through tracheal cannula. After about 30 minutes he regained consciousness. Following this episode, he developed fever of 40° C., and there were rhonchi throughout the lung fields. The tracheal cannula was left in place and d-tubocurarine was continued; and on many occasions following this the patient experienced, about 30 minutes after receiving d-tubocurarine, the same difficulties described above. At no time did he develop actual difficulty in respiratory exchange, his symptoms being entirely subjective. From this point the patient showed gradual improvement. After the fourth day of d-tubocurarine therapy, it became unnecessary to give the drug more than every six hours, dosage varying from 10 to 30 units. Five days after beginning treatment he could drink milk without difficulty, and was able to keep up his body fluid without the aid of intravenous therapy. Hemoconcentration had been guarded against throughout this period by maintaining a fluid intake of 3000 c.c. per day. A pyocyaneus urinary infection did not respond to sulfonamide therapy, but following streptomycin, 2 gm. per day for five days, the urine became clear. By the tenth day of treatment d-tubocurarine was no longer necessary and the muscle spasms had become infrequent and mild. Seventeen days after treatment was started, the patient was walking about the ward and at this time the tracheotomy cannula was removed. The wound in the neck healed rapidly. Moderately severe vertigo was thought to be secondary to toxicity to streptomycin. However, this improved gradually and three months after discharge it had entirely disappeared.

Discussion

Before the institution of treatment with d-tubocurarine this patient certainly appeared to be one with late onset of symptoms and a mild case of tetanus. It was decided that we should try to afford him relief of his painful muscle spasms by some method. At the time d-tubocurarine was first given we were not aware of such dramatic instances of bronchial spasm as had been reported by West.[4]

However, this has been one of the principal causes of death in experimental animals receiving d-tubocurarine, and it has been pointed out by numerous investigators that endotracheal catheters are required when prolonged curarization is necessary. The asphyxia which occurs has been ascribed mainly to (1) paralysis of the tongue, epiglottis, and false cords, (2) bronchospasm, (3) hypersecretion.[3] Atropine to prevent the hypersecretion was found to be dangerous, causing death probably by cardiac arrhythmias in curarized dogs.[7] Atropine was given to this patient without any clinical evidence of cardiac disturbances, but no electrocardiograms were obtained at the time. Of interest was the fact that after the tracheotomy was performed the patient often had a sensation of choking following an injection of d-tubocurarine. Certainly had not the tracheotomy tube remained in place repeated tracheal intubation would have been necessary. Another problem which caused a great deal of trouble was inability of the patient to void after receiving d-tubocurarine. This has not been reported in other cases, but in this particular patient urinary tract infection became very difficult to treat. As long as enough d-tubocurarine was given to prevent muscle spasms the patient was unable to contract his abdominal muscles, and at the same time distention of the bladder caused no urge to void. When it no longer became necessary to use large doses of d-tubocurarine, the ability to void gradually returned, and the residual urine disappeared with the improvement of the cystitis.

Another interesting feature was the patient's response to desensitization with tetanus antitoxin. His skin test, which had been positive both to the antitoxin and to normal horse serum, became negative the day following this desensitization and subsequently serum sickness did not appear during convalescence.

Summary

In summary, this represents a case of tetanus treated with d-tubocurarine and complicated by attacks of asphyxia and urinary retention. The chief difficulty was laryngospasm plus hypersecretion. It is obvious that one of the major dangers in the use of d-tubocurarine in this disease is the development of asphyxia and that a prophylactic tracheotomy may lessen this danger.

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MAJOR BLEEDING RESULTING FROM A SINGLE DOSE OF DICUMAROL *

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MULTIPLE doses of Dicumarol have frequently been reported to cause major bleeding episodes. On the other hand, it has been often emphasized [1, 2] that large single doses of Dicumarol given to normal animals and human beings cause marked prolongation of the prothrombin time but do not cause bleeding.

Herein is reported a case of major bleeding following a single dose of 300 mg. of Dicumarol in a patient with poor kidney function.

CASE REPORT

A 31 year old colored female was admitted to Grady Hospital on April 22, 1948, with the chief complaint of abdominal pain. Her illness had begun on April 11 with sharp pain above the umbilicus; this was continuous, severe, and persisted until some time after admission. At the onset she felt feverish but did not take her temperature; four days later, however, she had a hard, shaking chill, and thereafter a daily chill until admission. During the first week of her illness she noted frequency of urination and dysuria and from the eighth to the eleventh day had gross hematuria.

On admission to the hospital her temperature was 101° F.; the pulse rate was 112 per minute; respirations were 25 per minute; the blood pressure was 150 mm. of mercury systolic, 90 mm. diastolic. She appeared severely ill. Physical examination showed tenderness in the suprapubic region, in the epigastrium and in the left flank. On vaginal examination an irregular tender mass, fixed and slightly cystic, was felt in the left fornix, extending into the cul-de-sac and partially into the right fornix, which was thought to be a chronically infected tube. The ocular fundi were normal in appearance.

Blood examination showed 3,800,000 per cu. mm. erythrocytes, hemoglobin 9.9 gm. per 100 c.c., sedimentation rate (Westergren) 110 mm. per hour. The white cell count was 9,900 per cu. mm. with normal differential. The number of platelets in the blood smear was regarded as adequate. Test of the feces for occult blood was negative. The blood nonprotein nitrogen was 64 mg. per 100 c.c.

A cystoscopic examination was made. The bladder and urethral orifices were normal. Innumerable red blood cells were found in urine obtained from both pelves and in addition that from the left side contained many polymorphonuclear leukocytes in large clumps. The specific gravity of the bladder urine was 1.005, albumin 1 +, pH 5.5. Urine and blood cultures taken on admission showed no growth.

The initial clinical diagnosis was acute pyelonephritis with moderate impairment of renal function and subacute pelvic inflammatory disease. The patient was given penicillin 40,000 units every three hours intramuscularly. She also received sulfadiazine 1 gm. every six hours and sodium bicarbonate 2 gm. every six hours. In the hospital her temperature ranged between 101° and 104° F. On April 27 (five days after admission) her nonprotein nitrogen was 61 mg. per 100 c.c. and sulfadiazine level was 21 mg. per 100 c.c. Sulfadiazine administration was discontinued at this time. She had several chills during the first hospital week and her condition re-

* Received for publication June 25, 1949.

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mained about the same. On April 27 the temperature became normal but on May 3 it again rose to 101° F. On May 4 the patient suddenly complained of left anterior chest pain after turning over in bed. She did not cough up blood at the time and had no peripheral signs of thrombophlebitis. However, she became short of breath and was moderately orthopneic. On May 8 she coughed up pink frothy sputum which contained many red blood cells. There were signs of consolidation in the left lower lung and pleural friction rubs were heard in the lower axillary regions on both sides. Roentgen-ray examination of the chest at this time disclosed homogeneous consolidation of the left lower lung, interpreted by the radiologist as lobar pneumonia. Thoracentesis (left) at this time procured 500 c.c. of straw-colored fluid. The specific gravity was 1.017, and it contained 12,000 leukocytes and 5,000 erythrocytes per cu. mm. The differential count showed 60 per cent lymphocytes, 40 per cent granulocytes. Urine and sputum cultures taken that day grew *A. aerogenes.*

The clinical impression was that the patient was having septic pulmonary infarcts, probably coming from the deep pelvic plexus of veins. Accordingly, 0.25 gm. streptomycin was given every four hours.

On May 10, two days later, the prothrombin time was 20 seconds with a normal control plasma undiluted being 17 seconds, diluted to 30 per cent 27 seconds and to 20 per cent 34 seconds. Studies of the blood coagulation showed the clotting time to be 6.5 minutes, bleeding time 2.5 minutes. Red blood cell count was 3,470,000 per cu. mm., hemoglobin 12.8 gm. per 100 c.c. Liver function tests disclosed a total protein of 7.7 gm. per 100 c.c., formol gel reaction was positive, thymol turbidity 3.5 units and cephalin flocculation 2 + in 48 hours. The phthalein excretion was 2 per cent in one hour, non-protein nitrogen 66 mg. per 100 c.c.

TABLE I

Date	Patient	Control		
		100%	30%	20%
5–10	20*	17	27	34
5–11	23	15	25	31
5–12	1′ 25″	17	29	37
5–13	2′ 52″	16	28	37
5–14	2′ 37″	16	27	36
	8 p.m. 19.8	14.0	24.7	32.5
	12 p.m. 19.2	14.0	24.7	32.5
5–15	8 a.m. 17.1	14.0	24.7	32.5

* 300 mg. Dicumarol given after this prothrombin determination.

At this time the patient was given 300 mg. Dicumarol orally. The prothrombin times are recorded in table 1. From this it can be seen that the prothrombin time, essentially normal prior to administration of Dicumarol, was only slightly prolonged 24 hours later. After 48 hours, however, it became greatly prolonged, and remained essentially the same for the next three days.

During the two days succeeding Dicumarol administration the patient developed signs of increasing pleural effusion bilaterally. On May 13 ecchymoses were noted over the calves of both legs. Later in the evening more ecchymoses were seen on the extensor surfaces of both feet and hematomas were noted at the sites of intramuscular injections. On May 14 more of these areas were seen. The nonprotein nitrogen was 96 mg. per 100 c.c. The patient had generalized anasarca and increased dyspnea; she was cyanotic, somewhat lethargic and confused.

In order to shorten the prothrombin time, vitamin K_1 oxide (500 mg.) dissolved in 20 c.c. of 95 per cent alcohol and suspended in 5 per cent glucose in distilled water [2] was given intravenously at 12 noon on May 14. The first subsequent prothrombin time determination was made on blood drawn at 8:00 p.m. that evening; this and all subsequent prothrombin times were normal (table 1). No further ecchymoses developed following this. On May 15 thoracentesis revealed grossly bloody pleural fluid bilaterally, 1,100 c.c. being removed from the right and 600 c.c. from the left. The hematocrit on this fluid read 15 per cent.

The hemoglobin on May 15 was 7.8 gm. per 100 c.c. and the patient was transfused with 500 c.c. of whole blood.

There was no further evidence of bleeding, but the patient's condition continued to be poor. The temperature ranged from 101° F. to 103° F. and the white blood cell count remained elevated between 20,000 and 40,000 per cu. mm. Courses of sulfonamides, penicillin and streptomycin were without effect. The nonprotein nitrogen varied from 100 to 160 mg. per cent. Her condition became gradually worse over a period of one month. On June 17 she became stuporous and developed the clinical picture of terminal uremia. Death occurred on June 21.

An autopsy was performed four hours after death. The most striking finding at autopsy was periarteritis nodosa. This lesion was manifested in many ways. There was a focal myocardial necrosis, fibrinous pleuritis and pericarditis, acute ulceration of the esophagus and stomach with recent massive gastrointestinal hemorrhage and a localized peritonitis covering the broad ligament. The arterial lesions associated with these findings were generally very acute in nature and consisted of fibrinoid degeneration involving a part, or the entire circumference, of the arterial wall. In only one vessel was the response sufficiently marked and the necrosis sufficiently prominent to suggest early aneurysm formation. That this same process had occurred previously was suggested by the fact that many of the small vessels in the spleen showed lesions compatible with healed periarteritis nodosa and some of the larger vessels elsewhere showed a suggestion of previous thrombosis and recanalization prior to the new involvement by the degenerative process. The kidneys showed two interesting lesions. One of these involving the glomeruli suggested in some respects a picture of subacute glomerulonephritis. However, an earlier episode of periarteritis nodosa involving renal arteries and arterioles might well have explained this lesion. The vascular lesions and the absence of both acute and chronic glomerular lesions suggested this interpretation. The other lesion was a marked example of lower nephron nephrosis apparently due to sulfonamides. Probably secondary to the older glomerular lesion was a hyperplasia of the parathyroid glands.

Comment

The prothrombin time of 2′ 34″, fall in hemoglobin from 12.8 gm. per 100 c.c. to 7.8 gm., and occurrence of subcutaneous ecchymoses and bloody pleural fluid undoubtedly indicate that the patient suffered hemorrhage on the basis of Dicumarol-induced hypoprothrombinemia. The rapid reversal of this hypoprothrombinemia by the intravenous administration of vitamin K_1 oxide is in accord with previous experience in this clinic.[4]

In discussing the cause of the bleeding tendency in Dicumarol intoxication Link [2] noted that dogs with a prothrombin time of 10 minutes induced by a single dose of Dicumarol showed no tendency to hemorrhage; the same observation was made on rats and rabbits having prothrombin times in excess of 250 seconds on a 12.5 per cent plasma dilution. He concludes that there is some other factor in the bleeding tendency in addition to suspension of prothrombin activity.

Shumacker [5] has reported an incident in which a patient received 1,500 mg. of Dicumarol within 16 hours without evidence of hemorrhage. Stats and Bullowa [6] have administered single doses of 1,000 mg. without bleeding tendencies. Wright and Prandoni [7] in their study of Dicumarol dosage noted that 600 mg. given in a single dose had less toxic effect than when given in six doses of 100 mg. on successive days.

Richards and Steggerda [8] reported that unilateral nephrectomy did not influence susceptibility to Dicumarol. However, bilateral nephrectomy had a marked effect. Rats subjected to this procedure and given Dicumarol developed hypoprothrombinemia which was parallel to that of similarly treated, non-nephrectomized rats. These controls reverted to normal, whereas the prothrombin content of the nephrectomized rats continued to decrease until death four days later. No bleeding tendencies were noted. They concluded that although the kidney was not predominantly concerned with the metabolism of Dicumarol it must be assumed that some split product of Dicumarol leaves the body by way of the kidney.

Link [2] was unable to demonstrate Dicumarol in the urine by a spectrometric method after intravenous injection although it was detectable in the blood for 24 hours.

Bollman and Preston [9] produced renal damage in four dogs by the subcutaneous administration of uranium acetate, and administered 10 mg. per kg. of Dicumarol. The prothrombin time was depressed to below 6 per cent for 8, 13, 14, and 15 days. No mention of bleeding tendency was made. However, when total anuria was produced by ligating both ureters in one dog and by bilateral nephrectomy in a second and the same dose of Dicumarol administered, both dogs died in three days of peritoneal hemorrhage.

The dose of Dicumarol used in this case is a standard dose. Some authors [5] have suggested an initial dose of 400 mg.

Vascular damage in periarteritis nodosa and chronic nephritis is known to produce bleeding. However, the concurrent cessation of hemorrhage and hypoprothrombinemia produced by the administration of vitamin K_1 oxide strongly suggests that the Dicumarol factor was of primary importance.

The results of the liver function tests and the response to vitamin K indicate no significant abnormality of liver function. Kidney function tests were grossly abnormal and because of this it is not felt that this case contradicts Link's hypothesis of additional factors being present in Dicumarol induced hemorrhage besides hypoprothrombinemia. On the other hand, it is suggested that this additional factor may be provided by continued exposure to one small dose of Dicumarol when there is marked impairment of renal function.

Summary

Severe hemorrhages occurred in a patient with poor kidney function following a single dose of 300 mg. of Dicumarol. The prothrombin time was prolonged to more than 2.5 minutes at the time of the bleeding. Treatment with vitamin K_1 oxide reversed the Dicumarol effect, and hemorrhages ceased. This is believed to be the first report of bleeding following one dose of Dicumarol in a human being.

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LONG TERM DICUMAROL THERAPY *

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Ground work in the use of Dicumarol for preventing the extension of coronary thrombosis and the development of mural thrombi in the presence of myocardial infarction was laid by Solandt, Nassim, and Best [1] in 1938. Using the anticoagulant, heparin, they were able to prevent the formation of coronary thrombi and intracardiac mural thrombi when deliberate experiments were performed to produce these lesions in experimental animals.

With the advent of Dicumarol numerous workers [2, 3, 4] began its use in the treatment of coronary thrombosis with myocardial infarction and its complications.

Recently the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction has published the results of a survey of 1000 patients half of whom received Dicumarol. Significantly lower mortality rates were reported.[5] One other factor receiving further study by the committee was the length of time Dicumarol should be continued following a thrombo-embolic episode. They state "unless contra-indica-

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tions arise, the Dicumarol therapy should be continued in the chosen cases over a minimum period of 30 days, preferably 30 days after the last thrombo-embolic episode." [5] That the committee recognized that the time limit stated may fail to relieve certain situations is attested to by its chairman's report on "long term" Dicumarol therapy and his citing of attempts of others [6] to continue Dicumarol therapy for as long as 36 months.

The following case report details our experiences in the continuous use of Dicumarol for 40 months with one near disastrous intermission. It also records the experiences of one of us (JSA), the patient, in his personal use of the drug over this period.

Case Report

First Hospital Admission. A 48 year old white male physician was admitted to the Mt. Sinai Hospital on May 22, 1944. Eleven hours prior to entrance the patient had suffered an attack of severe precordial pain with dyspnea and shock. There was a previous history of slight anginal pain for the past several years. When hospitalized, the patient complained of substernal pain and distress. He was slightly dyspneic and pale. Pulse was regular, rate 100. Blood pressure was 108 mm. Hg systolic and 70 mm. diastolic. Heart tones were of fair quality. A clinical diagnosis of acute myocardial infarction was made.

Hospital Course. The patient was placed on a regime of oxygen, dilaudid, papaverine, aminophyllin and complete bed rest for the relief of substernal pain and restlessness of which he frequently complained. He ran a sustained fever of 99 to 105° F. for the first seven hospital days after which he was afebrile.

On May 25, 1944 examination revealed a systolic bruit along the left sternal border which had disappeared by May 27. A few coarse râles were heard over both lung bases posteriorly on May 25 but had disappeared on the following day.

Varicose veins of a moderate type had been present in both legs for years, and ace bandages were applied on the first hospital day and daily massages and passive exercises were performed until dismissal.

The patient improved and was discharged on July 3, 1944.

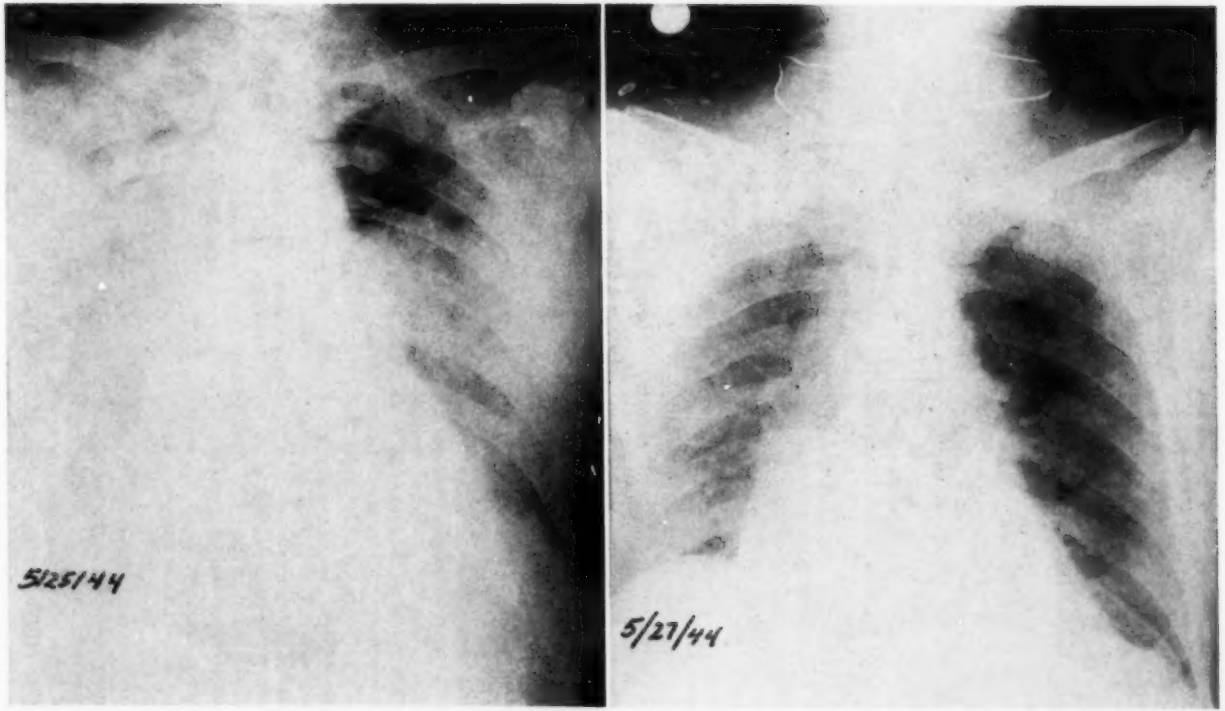
Laboratory Data. Red blood cells 4,540,000; hemoglobin 15 gm.; color index 1.0; white blood cells 18,300; per cent non-segmented polys 29; per cent segmented polys 51; per cent lymphocytes 14; per cent monocytes 6. The erythrocyte sedimentation rate (Wintrobe) ranged from 13 mm. on admission to 42 mm. on dismissal.

Electrocardiogram on May 24, 1944 revealed ST changes compatible with recent acute anterior myocardial infarction. Serial electrocardiograms disclosed evolution of an anterior wall infarction with a subsequent healing pattern.

Chest roentgenogram on May 24, 1944 revealed diffuse mottling of the entire right lung. The lower two-thirds of the left chest was also involved. The roentgen appearance of the chest was interpreted as a bilateral bronchopneumonic process or changes secondary to pulmonary infarction. Reëxamination on May 27, 1944 revealed clearing of most of the infiltrations. Hilar infiltrations were still present. Both examinations were done at the bedside and accurate estimates of heart size were impossible although the transverse diameter of the heart appeared grossly enlarged.

The patient made a prolonged recovery and felt fairly well with the exception of occasional precordial pain on exertion which was alleviated by sublingual nitroglycerin tablets gr. 1/150.

On May 20, 1945, one year later, the patient noted fever and pain in the chest exaggerated by deep inspiration and swallowing which persisted for two days and then subsided. There were no electrocardiographic changes or chest x-ray abnormalities at that time.



A B

FIG. 1A. Marked increase in density involving the entire right lung and greater portion of left lung due to pulmonary infarction.
FIG. 1B. Almost complete resolution of density in right lung and complete disappearance of increased density in left lung two days later.

On July 22, 1945 the patient noted vague precordial distress and on July 23 he experienced retrosternal pain which radiated into the left arm. The pain was exaggerated by deep inspiration.

Second Hospital Admission. The patient was readmitted to Mt. Sinai Hospital on July 24, 1945 with substernal pain exaggerated by deep inspiration. Blood pressure was 100/80. Pulse was regular, rate 120. Temperature 100° F. Heart tones were distant. A clinical diagnosis of myocardial infarction with pleuro-pericardial involvement was made.

Hospital Course. Nitroglycerin, papaverine, pantopon, oxygen, and, for the first time, Dicumarol were instituted in dosages adequate to keep prothrombin levels between 40 and 50 per cent for the duration of his hospital stay.

The patient continued to have chest pain and spiked temperatures to 101° F. for the first two days of his admission after which he remained afebrile. Examination of the lungs on July 26, 1945 revealed scattered râles over the right base posteriorly. A diagnosis of pulmonary infarction secondary to mural thrombi (arising from the right ventricle) or from phlebothrombi of the lower limbs was made. Frequent examinations, however, failed to reveal any evidences of superficial or deep vein thrombosis. Penicillin was instituted prophylactically. The patient was dismissed on August 6, 1945 and Dicumarol was discontinued.

Laboratory. Red blood cells 4,500,000; hemoglobin 14 gm.; white blood cells 16,800; per cent non-segmented polys 31; per cent segmented polys 57; per cent lymphocytes 7; per cent monocytes 5; urinalysis negative. Erythrocyte sedimentation rate (Wintrobe) 43 mm. on admission. Prothrombin times ranged from 75 per cent on admission to 36 per cent on dismissal. Following institution of Dicumarol all prothrombin levels were kept below 48 per cent.

Serial electrocardiograms revealed chronic coronary insufficiency of the anterior wall.

Chest roentgenogram on July 25, 1945 in the antero-posterior position at the bedside: the right half of the diaphragm was elevated to the level of the fourth rib anteriorly. The heart was displaced to the right and its right border was situated at least 9 cm. to the right of the midline. The trachea was also shifted to the right for a distance of 2.5 cm. Several areas of increased density, some linear, were present in the lower two-thirds of the right lung.

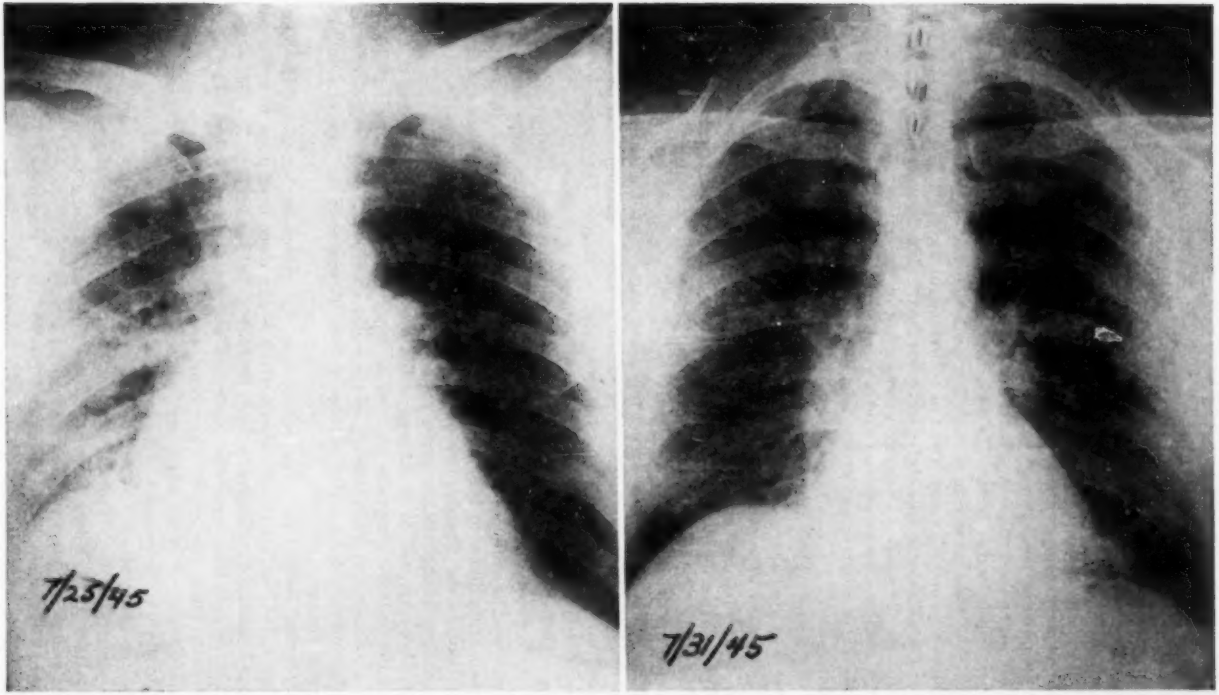
The left lung was clear and relatively emphysematous.

Reëxamination of the chest on July 27, 1945 revealed improvement in the degree of atelectasis. The right half of the diaphragm was situated at a lower level. Infiltrations were noted in the lower half of the right lung especially in the regions close to the diaphragm. Only the lower trachea deviated somewhat to the right. There was 1 or 2 cm. less of the right cardiac border on the right side of the chest than on the previous examination.

Reëxamination of the chest by means of a teleroentgenogram on July 31, 1945 revealed no evidences of pulmonary infiltration, pneumonitis or atelectasis in the right lung. There was a small patch of increased density in the left lung region adjacent to the apex of the left ventricle. The heart size, shape and position were within normal limits. No roentgen evidence of left ventricular enlargement was present. The trachea was in the midline.

On the basis of these changes over a period of four to six days an interpretation of atelectasis of the right lung secondary to bronchostenosis was made. Clinically, however, the patient expectorated no blood or sputum which could account for the rapid clearing of the roentgen findings. Pulmonary infarctions were considered by the clinicians to be responsible for the morbid x-ray findings.

Third Hospital Admission. The patient was readmitted to Mt. Sinai Hospital on September 21, 1945 with an acute episode of chest pain similar to that experienced



A B

FIG. 2A. Mottled density in right lower lobe due to pulmonary infarction seen on second admission (July 25, 1945).
FIG. 2B. Complete disappearance of changes due to infarction except for slight increase in bronchovascular markings in the right base six days later (July 31, 1945).

on the last hospital admission and marked by pain in the right and left hemithorax aggravated by the slightest motion.

Dicumarol had been discontinued on August 6, 1945, the day of the patient's last hospital dismissal.

The patient related that he had had similar episodes on the eighteenth to twentieth of each month since May 1945 with the exception of June.

Physical findings again revealed an atelectasis and pneumonitis of the right lung. Hemogram, sedimentation rate and serial electrocardiograms were essentially the same as on the previous admissions. Roentgen examination of the chest in the antero-posterior position at the bedside again revealed atelectasis of a segment of the right middle or right lower lobe or both. The signs were not as marked as noted previously on July 25, 1945. Reëxamination of the chest on September 26, 1945 revealed a few residual infiltrations and plate-like areas of atelectasis in the right lower chest. The right half of the diaphragm was still slightly elevated. The heart and trachea were slightly shifted to the right. Moderate enlargement of the left ventricle of the heart was apparent on the roentgenograms and was observed during fluoroscopy. There was no evidence of enlargement of the left auricle with the esophagus outlined by barium sulfate.

Hospital Course. The patient was given supportive therapy but Dicumarol was omitted. He was discharged on September 29, 1945. As on previous hospital stays his first hospital days were marked by a daily fever of 99 to 102°.

Fourth Hospital Admission. The patient was examined at the Mayo Clinic in October 1945 and developed an acute exacerbation with a typical attack during his survey. On October 7 he developed severe chest pain with a remitting type of fever which persisted for five days.

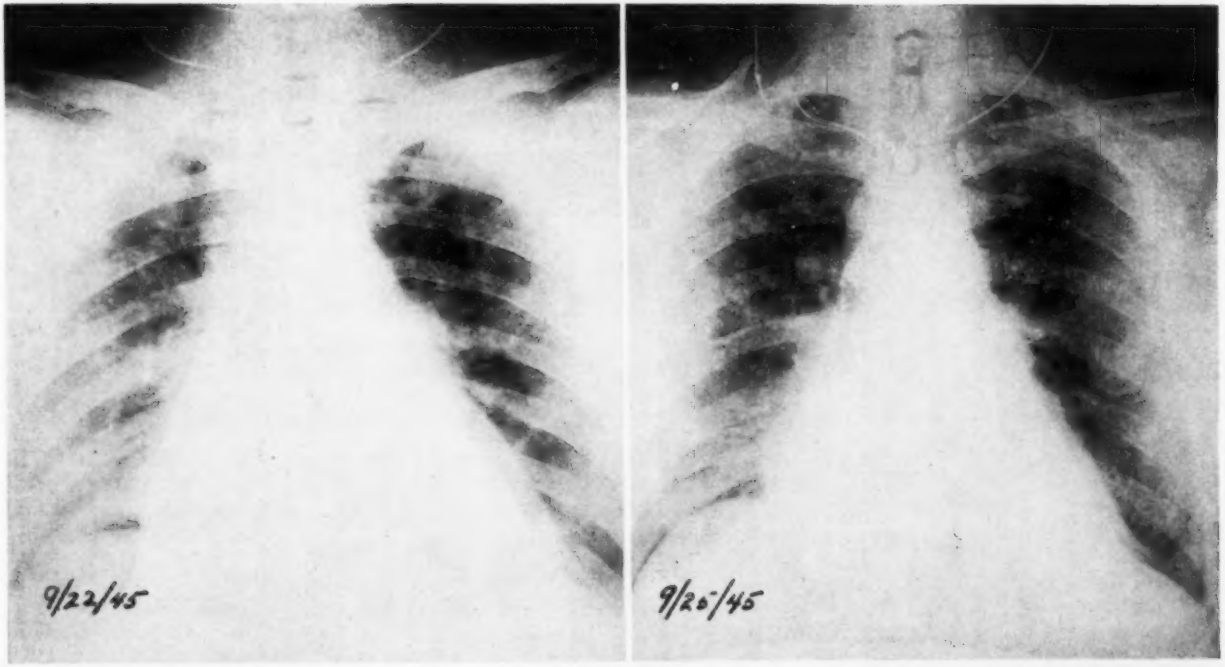
Significant laboratory finding during this acute stage was a leukocytosis reaching a maximum of 17,900 on the fifth day of the patient's illness. Examination of a blood smear showed myeloid immaturity to the promyelocyte stage. These changes were regarded as indicative of a leukemoid reaction although a primary blood dyscrasia could not be excluded. Repeated chest x-rays were made but they failed to afford any conclusive evidence of pulmonary pathology. Two blood cultures were done with negative results. The sedimentation rate rose from 55 mm. per hour on the first day of the patient's acute illness to 102 mm. per hour on the tenth day. It then receded to 58 mm. per hour on the fifteenth day of his illness. Electrocardiograms showed no significant changes throughout the course of the illness.

Drs. R. D. Pruitt and A. R. Barnes of the Mayo Clinic concurred that the explanation of the patient's symptoms was due to recurrent pulmonary emboli probably multiple in an attack and likely arising in the right ventricle. They suggested that Dicumarol be continued for a period of three or four months with the hope of avoiding these recurrent episodes.

Fifth Hospital Admission. The patient was readmitted to Mt. Sinai Hospital on September 4, 1947 with a similar attack which began three days prior to entrance. He had taken Dicumarol continuously from October 7, 1945 until June 18, 1947 when it was decided that a trial would be made without the drug. Blood pressure was 120/80. Regular pulse rate of 80. The heart tones were distant.

Hospital Course. Patient was placed on oxygen, sedated, and Dicumarol was again initiated. Several episodes of retrosternal pain marked his first few hospital days and he ran a low grade fever 99 to 100° for the first five days. He was dismissed on October 3, 1947. With the exception of a leukocytosis and a sedimentation rate ranging from 34 to 38 mm. (Wintrobe) his laboratory findings including electrocardiograms and chest x-rays revealed little or no change.

The patient has remained on Dicumarol therapy since that time. His course is



A B

FIG. 3A. Evidences of pulmonary infarction in right base on third admission (September 22, 1945).
FIG. 3B. Marked resolution with residual streak-like densities in right base three days later (September 25, 1945).

marked by retrosternal pain on exertion but no recurrences of these thromboembolic episodes have recurred since September, 1947.

Personal Observations by J. S. A. Long term Dicumarol therapy was initiated on October 7, 1945 and continued until June 18, 1947. It was restarted on September 4, 1947 because of a recurrence of a thromboembolic phenomenon. From November 3, 1945 until June 12, 1946 biweekly prothrombin times were taken to determine adequate dosage. A weekly dosage totalling 500 to 550 mg. was necessary to maintain the prothrombin level within optimal limits. By September 1946 a pattern of individual response to Dicumarol seemed fairly well established and weekly, then biweekly and occasionally monthly estimates were made. By October 1947 the pattern had become so firmly established that it was possible to predict estimates within several points of the actual prothrombin level.* Records kept since that time of the predicted and actual levels reveal little disparity between the two. The administration of a 100 mg. dose of Dicumarol followed by two or three daily doses of 50 mg. Dicumarol (450 to 500 mg. per week) obtained prothrombin levels between 37 per cent and 18 per cent from November 1, 1947 to the present time. The lower levels occurred only during periods when I received aspirin or sulfonamides. Dicumarol dosage has been since readjusted to avoid critically low levels during periods when these drugs are being taken. This phenomenon became apparent late in 1946 when I began to note gingival bleeding (bloody toothbrush) during a period when my usual Dicumarol medication was supplemented by aspirin and sulfonamides. This sign had repeatedly occurred before its significance was realized and mirrored the low prothrombin levels which were demonstrated at that time.

Besides a bloody toothbrush, petechiae, conjunctival hemorrhages, ecchymosis of the skin, hematuria and bloody stools also occurred.

Mild gastrointestinal disturbances seem to precede the onset of hemorrhagic phenomena and consist of distention, flatulence, abdominal cramps and light to clay colored stools.

These episodes have been avoided by reducing Dicumarol dosage during salicylate or sulfonamide therapy.

A total of 66,300 mg. of Dicumarol has been taken over a period of 40 months.

Discussion

The patient described experienced numerous episodes of coronary insufficiency with myocardial infarctions. Complicating the episodes were frequent pulmonary infarctions which appeared from the evidence on hand to arise from the right ventricle.

These episodes occurred on May 22, 1944 (the initial attack); May 22, 1945; July 23, 1945; August 18, 1945 and September 20, 1945. Dicumarol was used during one hospital stay from July 24, 1945 to August 6, 1945.

With the discontinuance of the Dicumarol, another attack occurred about six weeks later on September 20, 1945. Constant use of Dicumarol from October 7, 1945 to June 18, 1947 prevented further instances of coronary thrombosis or pulmonary infarctions. When Dicumarol was discontinued after 20 months a further episode three months after its discontinuance occurred.

Re-administration of Dicumarol since that time has prevented further attacks.

* The prothrombin determinations on all occasions were done after the method of Ziffren et al.[7, 8] This simple "bedside test" utilizes whole blood to which thromboplastin solution is added. The clotting time is observed and compared with a normal control, permitting the results to be expressed in reference to a normal standard. The test has been found to be accurate enough for routine clinical use.

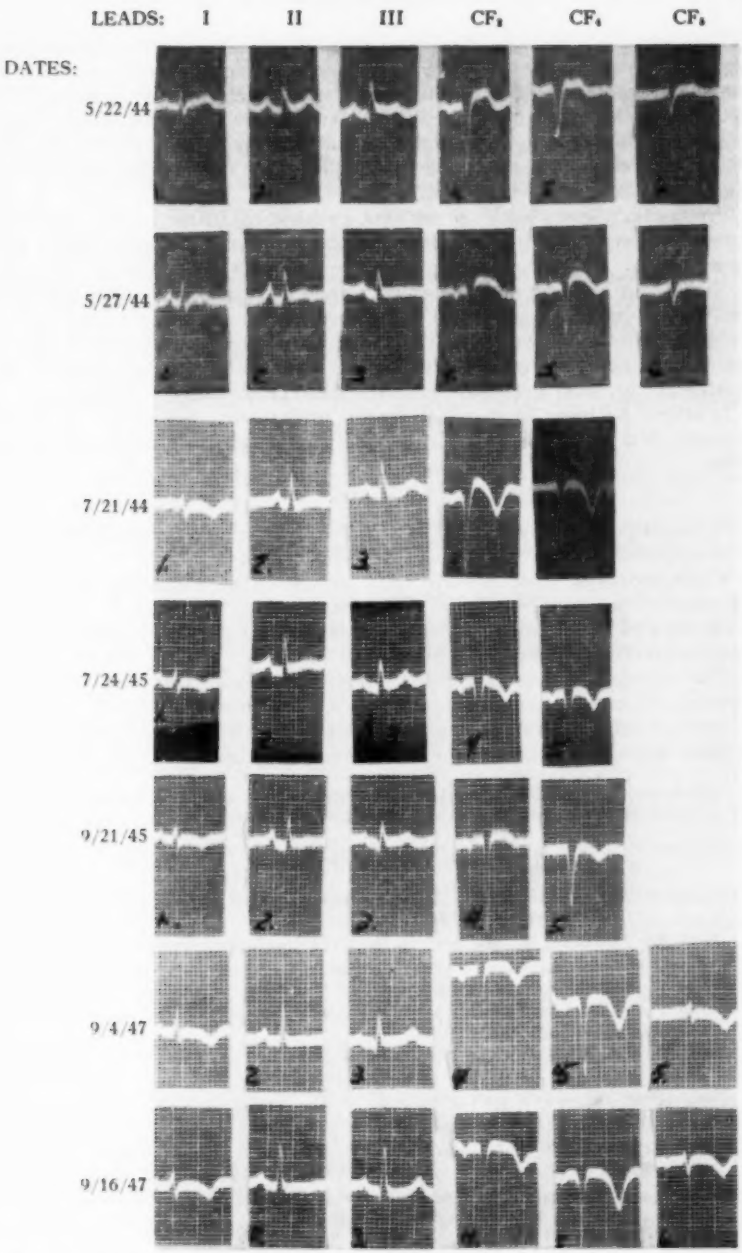


FIG. 4. Electrocardiograms illustrating changes on various hospital admissions. The tracings indicate changes compatible with anterior wall infarction.

The exact mechanism for the almost monthly episodes of embolic phenomena may be only surmised. They may have been coincident with the patient's increased activity one month following each attack leading to fresh myocardial infarctions with or without actual coronary thrombi; or intramural thrombi may have required a month to attain both size and friability. Whatever the mechanism, the thromboembolic phenomena were altered by anticoagulant therapy and recurred on Dicumarol withdrawal.

Prothrombin levels below 50 per cent (method of Ziffren et al.) and above 20 per cent prevented thromboembolic episodes and avoided hemorrhagic phenomena.

Nichol and Fassett [9] pointed out that while individuals may alter their sensitivity to Dicumarol, only slight variations occur once the required dose is established after a few weeks' observation. Their remarks hold true in this instance. The effects of various drugs used concurrently with Dicumarol in depressing prothrombin levels have been remarked on by many investigators.

It should be reëmphasized that careful prothrombin laboratory checks are necessary, first at daily, and then at gradually longer intervals not exceeding two weeks.

Summary

A patient has been given 66,300 mg. of Dicumarol over a period of 40 months.

A consistent pattern of Dicumarol response has occurred.

Thromboembolic episodes have been terminated by Dicumarol administration and have recurred on withdrawal of the drug.

Anticipated prothrombin levels based on the amounts of Dicumarol taken approximate closely the actual prothrombin levels.

The depressant effect of salicylates and sulfonamides have been noted and symptoms of early hemorrhagic tendencies have been demonstrated.

No harmful effect of Dicumarol administration over this prolonged period has been noted when prothrombin levels were kept between 20 and 50 per cent.

Addendum. Dicumarol has now been administered for a total of 51 months with no recurrent thromboembolic episodes and no hemorrhagic phenomena.

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NEUTROPENIA ASSOCIATED WITH SPLENOMEGALY AND ATROPHIC ARTHRITIS (FELTY'S SYNDROME): REPORT OF A CASE IN WHICH SPLENECTOMY WAS PERFORMED *

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The syndrome of atrophic polyarthritis occurring in an adult, associated with fever, secondary anemia, leukopenia and splenomegaly, was described by Felty [1] in 1924. Chevallier [2] suggested in 1930 that splenectomy might produce relief of the arthritis in Felty's syndrome. This surgical procedure, however, was not performed until 1932, when Hanrahan and Miller [3] reported the first case of Felty's syndrome in which splenectomy was performed for the neutropenia and splenomegaly. Subsequent cases of the syndrome under discussion in which splenectomy was performed were reported by Craven [4]; Reich [5]; Bloem, van Creveld, Kuipers and Zuidema [6]; Steinberg [7]; Gyntelberg [8]; Trolle and Trolle [9]; Dameshek [10]; Zimmer [11]; Hirschboeck [12] (two cases); and Doan [13] (two cases). These reports include a total of 13 cases of Felty's syndrome in which splenectomy was performed. The patients of Reich and Gyntelberg and one of the patients on whom Hirschboeck reported died postoperatively, but in the majority of the others the associated neutropenia was benefited by splenectomy. Arthritis was improved in the cases of Hanrahan and Miller; Craven; Bloem, van Creveld, Kuipers and Zuidema; Zimmer; and in one of Hirschboeck's cases.

In Steinberg's reported case, splenectomy proved of value after other methods of treatment had proved ineffectual. This author stated that studies of bone marrow were necessary and, if inactivity of the bone marrow was observed, he believed that splenectomy could not possibly be of value. Hirschboeck in 1946 presented the data on two cases of Felty's syndrome in which splenectomy was performed. One patient survived five years, while the other died six weeks after splenectomy. In each of these cases splenectomy resulted in a return of the peripheral blood picture to normal limits. Hirschboeck discussed the two concepts that have arisen to explain the pathogenesis of the leukopenia in the syndrome of pancytopenia. The hormonal hypothesis presumes that the greatly enlarged spleen produces a hormone which suppresses the maturation of blood cells in the marrow and their release to the blood. The phagocytic hypothesis presumes that the blood changes in the pancytopenic syndrome are due to in-

* Received for publication October 12, 1948.

creased phagocytic activities of an enlarged spleen. Hirschboeck expressed the opinion that the leukopenia in Felty's syndrome could not be adequately explained by either the hormonal or the phagocytic hypothesis alone, but stated that the answer might eventually be found in a combination of the two hypotheses.

The concept that leukopenia might result from splenomegaly of various origins was first suggested by Bauer [14] in 1899. The term "hypersplenism" was first used by Eppinger [15] in 1913. While in isolated cases neutropenia had been treated by splenectomy prior to 1939, it remained for Wiseman and Doan [16] in that year to renew interest in the group of cases with chronic neutropenia associated with splenomegaly. In 1939 they [16] first advanced their concept of primary splenic neutropenia and in 1942 they [17] reported in detail five cases of this syndrome. Joint pain and swelling were observed in two of the cases of primary splenic neutropenia reported by Wiseman and Doan. Subsequent cases fulfilling the requirements of primary splenic neutropenia and in which the condition was treated successfully by splenectomy have been reported by the following authors: Salzer, Ransohoff and Blatt [18]; Rogers and Hall [19]; Langston, White and Ashley.[20] The patient on whom Langston, White and Ashley reported had suffered with atrophic arthritis for six years, and these authors had considered the diagnosis of Felty's syndrome. Improvement of the arthritis was observed after splenectomy in this case.

The similarity of the clinical syndromes of Felty's syndrome and primary splenic neutropenia is apparent. Both of these syndromes have in common neutropenia and splenomegaly. Panhyperplasia of the bone marrow, which is characteristic of primary splenic neutropenia, is not constantly observed in cases of Felty's syndrome. Swelling of the joints was observed in two of the five cases of primary splenic neutropenia recorded by Wiseman and Doan, and in one case of this syndrome recorded by Langston and associates. It is noteworthy that in the case of primary splenic neutropenia previously reported by Rogers and Hall atrophic arthritis has subsequently developed. This was observed for the first time in October, 1947, five years after splenectomy had been performed with beneficial results for primary splenic neutropenia. Levy [21] has recently reviewed the syndrome of granulocytopenia associated with atrophic arthritis (Felty's syndrome). In view of the marked improvement in cases of primary splenic neutropenia in which splenectomy has been performed it seems logical to evaluate the same procedure in cases of Felty's syndrome.

It is the purpose of this report to present the clinical findings in a case of atrophic arthritis with splenomegaly, anemia and neutropenia, in which splenectomy was performed. The preoperative presence of a hypoplastic sternal bone marrow, with return of the sternal marrow to normal after splenectomy, is of special interest in this case.

Case Report

The patient was a white adult male physician, aged 67 years. When we examined him for the first time on June 19, 1947, he complained chiefly of weakness and neutropenia. For 24 years the patient had observed progressive evidence of atrophic arthritis, which had involved the fingers, hands, elbows, toes, feet and knees. The joint manifestations were so extreme that for two years he had been incapacitated. Recent activity of arthritic symptoms, with joint pain and swelling, had been observed. Five months prior to our examination a routine examination of the blood cells had

revealed neutropenia. Leukocytes had numbered 2,500 per cubic millimeter of blood with 23 polymorphonuclear leukocytes per 100 white blood cells. Since this examination the leukocyte counts had ranged from 1,450 to 2,400 per cubic millimeter of blood. Associated with the development of the neutropenia there were increasing exhaustion and fatigue. These symptoms were so severe that the patient was confined to bed most of the time. He had received iron, liver extract, yellow bone marrow extract and four blood transfusions without improvement of the leukocyte count. There was progressive loss of weight, estimated at 25 pounds (about 11 kg.). The past medical history revealed that the patient had undergone tonsillectomy, appendectomy and hemorrhoidectomy. There were no major medical illnesses and no chronic illnesses other than atrophic arthritis. There was no history in the past of bleeding or purpuric manifestations.

FIG. 1. Roentgenogram of the hand. Advanced rheumatoid arthritis.

The physical examination revealed an elderly white man, with advanced atrophic arthritis. The pulse rate was 70 beats per minute and the temperature was 98° F. The blood pressure was 110 mm. of mercury systolic and 80 diastolic. The eyes, ears and nose were normal. There was a deep region of ulceration measuring 2 by 2 by 4 mm. in the anterior portion of the hard palate. The physical examination of the heart and lungs did not reveal any abnormalities. The examination of the abdomen revealed splenomegaly, with enlargement to a distance three fingers'-breadth below the costal margin. The liver edge was not palpable. The joints of the upper and lower extremities were deformed and ankylosed by advanced atrophic arthritis. A diagnosis of atrophic arthritis with leukopenia and splenomegaly (Felty's syndrome) was made.

Roentgenograms were made of the chest, hands and feet. The examination of the chest revealed clear lung fields. There was torsion of the arch of the aorta with

a small linear plaque present. The transverse diameter of the heart was 17.0 cm. as compared with the transverse diameter of the thorax which was 32.0 cm. The roentgenographic examination of the hands revealed marked generalized osteoporosis. There was narrowing of the radiocarpal joint spaces and sclerosis about the adjacent articular margins. There was complete dislocation at all of the metacarpophalangeal joints. The proximal phalanges were displaced beneath the corresponding metacarpal heads and deviated toward the ulnar side of the hand (figure 1). There were no regions of bone destruction. The roentgenographic examination of the feet revealed generalized osteoporosis. There were lateral deviation of the toes and partial subluxation of the metatarsophalangeal joints (figure 2). An electrocardiogram was interpreted as being within normal limits.

FIG. 2. Roentgenogram of the feet. Advanced rheumatoid arthritis.

The results of blood counts made prior to splenectomy are recorded in table 1. The following additional laboratory tests were made. The reaction of the urine was acid and the specific gravity was 1.018. The albumin was recorded as grade 1 (on the basis of 1 to 4 with 1 representing the least and 4 the greatest degree of severity). Sugar was not observed in the urine. The microscopic examination of the urine revealed 1 to 5 leukocytes per high power field. The Kahn reaction was negative. The results of routine agglutination tests for typhoid fever, paratyphoid fever and undulant

fever were negative. The blood type was O, with positive Rh factor. The reticulocyte count was 2.7 per cent. The erythrocyte fragility test revealed beginning hemolysis at 0.48 per cent and complete hemolysis at 0.38 per cent, as compared with a control which revealed hemolysis beginning at 0.44 per cent and complete at 0.38 per cent. The bromsulfalein test revealed 45 per cent retention of the dye five minutes after its administration with no excretion 30 minutes after the administration of the dye.

Aspiration of the sternal bone marrow revealed a markedly hypocellular marrow. There was a relative increase of normal plasma cells. There appeared to be a quantitative reduction of both nucleated erythrocytes and granulocytic leukocytes. It is possible that the apparent degree of hypoplasia may have been intensified by an admixture of blood from the venous sinuses, but even allowing for this dilution the quantitative reduction was apparent.

TABLE I

Blood Counts and Values for Hemoglobin before Operation

Date, 1947	Leukocytes per cu. mm. of blood	Erythrocytes, millions per cu. mm. of blood	Platelets, per cu. mm. of blood	Hemoglobin, gm. per 100 c.c. of blood	Leukocytes, per cent					
					Segmented polymorphonuclears	Stab forms	Lymphocytes	Monocytes	Eosinophiles	Basophiles
1:10	2,500	4.59	—	15.3	23	—	71	2	4	—
2:8	2,250	—	—	—	21	1	74	—	4	—
2:24	1,450	4.60	—	14.0	44	—	49	6	1	—
3:3	2,300	—	—	—	9	—	79	1	10	1
5:31	2,100	4.21	—	15.0	28	—	58	1	13	—
6:19	1,[illegible]0	4.34	—	11.5	22	3	60	—	15	—
8:23	1,600	4.90	—	14.5	21	—	72	—	7	—
9:27	1,750	4.21	—	16.4	15	—	80	—	5	—
11:8	1,650	3.74	—	12.7	24	—	71	1	3	1
11:13	1,300	3.56	—	11.5	39	10	49	—	2	—
1948										
1:6	2,450	3.35	—	11.5	31	—	60	1	8	—
1:15	2,200	3.70	—	11.2	20	8	55	1	15	1
1:15	2,200	3.70	—	11.2	20	8	55	1	15	1
1:17	1,750	3.24	207,360	10.5	17	5	66	1	10	1
1:22	1,600	3.60	—	11.2	35	8	44	2	8	3

Administration of ferrous sulfate, vitamin B complex and folic acid was begun. Crude liver extract was administered by intramuscular injection. Under this regimen no improvement of the leukocyte count was observed. There was progressive fatigue. Five months after the examination hypochromic anemia was observed to have developed. This was followed by unexplained fever, with the temperature ranging from 103° to 104° F. for one week. Subsequently there developed large regions of ulceration, measuring up to 3 cm. in diameter, over the deformed metacarpal and metatarsal joints. These regions of ulceration were resistant to penicillin, administered intramuscularly and locally. Fatigue increased, so that the patient was confined completely to bed. In view of the progressive fatigue, neutropenia, ulceration of the joints and anemia, splenectomy was advised. This procedure was recommended with hesitation in view of the hypoplastic sternal marrow, but in view of the progressive decline experienced by the patient it appeared to offer the only chance for improvement. This decision received support in a personal communication from Dr. Charles A. Doan [22] relative to the beneficial experiences that he had observed after splenectomy in patients afflicted with Felty's syndrome, provided the bone marrow was hyperplastic.

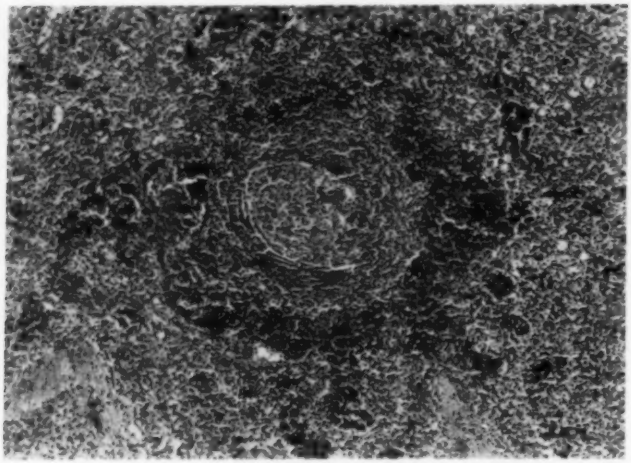

FIG. 3. Section of spleen. Perifollicular congestion. (H and E, × 80.)

The patient was hospitalized in St. Anthony's Hospital. On January 23, 1948, splenectomy was performed by Drs. F. H. Langley and R. W. S. Owen. The spleen, which was greatly enlarged, measured 20 by 11 by 6 cm. and weighed 910 gm. The liver and the pancreas were normal to palpation and inspection. No accessory spleens were observed.

The operative procedure was completed without complications. During the operation an attempt was made to aspirate blood from both the splenic artery and the splenic vein, in order to demonstrate any variation of the leukocyte counts.

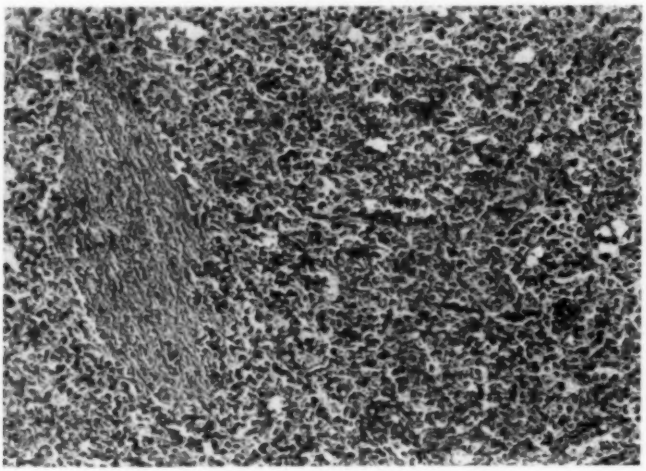

FIG. 4. Section of spleen (× 160). Red pulp.

Blood for a leukocyte count was obtained from the splenic artery, but technical difficulties prevented the surgeons from obtaining blood from the splenic vein. Blood from the splenic artery contained 7,400 leukocytes per cubic millimeter of blood. In view of the fact that peripheral blood prior to operation contained 1,600 leukocytes per cubic millimeter of blood, the elevated count obtained from splenic arterial blood may be significant.

The histologic examination of sections of the spleen revealed severe congestion (figure 3*a* and *b*). This was most prominent in the perifollicular regions. Some increase of the connective tissue was present. No demonstrable evidence of phagocytosis of the polymorphonuclear leukocytes by the reticulo-endothelial elements could be demonstrated in fixed tissue preparations of the spleen.

TABLE II

Blood Counts and Values for Hemoglobin after Operation

Date, 1948	Leukocytes per cu. mm. of blood	Erythrocytes, millions per cu. mm. of blood	Platelets per cu. mm. of blood	Hemoglobin, gm. per 100 c.c. of blood	Leukocytes, per cent					
					Segmented polymorphonuclears	Stab forms	Lymphocytes	Monocytes	Eosinophiles	Basophiles
1:23 10 a.m.	3,000	—	—	—	37	20	41	—	2	—
1:23 2 p.m.	4,000	—	—	—	51	8	36	1	3	1
1:23 7 p.m.	3,050	—	—	—	62	4	30	—	4	—
1:24	7,150	4.17	325,200	11.2	76	8	12	4	—	—
1:25	5,400	3.90	—	10.5	40	22	33	—	4	1
1:27	4,850	4.60	478,400	11.9	57	9	34	—	—	—
1:29	5,150	4.04	—	11.2	56	4	29	—	9	2
2:2	4,750	4.27	452,600	—	46	5	44	1	4	—
2:4	3,800	4.30	—	12.7	53	4	30	—	13	—
2:6	3,000	4.20	—	13.6	28	2	67	—	3	—
2:9	2,250	3.73	—	13.0	32	—	50	2	14	2
2:12	3,750	4.22	—	14.7	40	—	55	1	4	—
2:20	3,900	4.42	—	14.0	50	—	45	1	2	2
2:27	3,550	4.92	—	16.0	30	—	61	—	8	1
3:5	3,600	4.69	—	16.8	26	4	61	2	7	—
3:12	3,850	4.91	—	16.4	26	—	65	—	8	1
3:19	3,700	4.77	—	16.0	22	—	77	1	—	—
4:5	3,300	5.80	—	18.0	25	—	66	—	9	—
5:5	3,000	4.47	—	19.2	12	—	79	—	9	—
5:27	4,950	5.66	—	16.7	18	—	72	2	8	—
6:16	5,700	4.83	—	15.5	7	—	84	—	9	—
7:9	4,400	4.59	—	18.0	15	—	79	—	5	1
8:3	4,500	4.54	—	18.5	21	—	70	—	9	—
8:16	4,350	4.54	—	16.5	13	—	83	—	4	—
9:6	4,400	4.79	—	19.2	13	—	79	1	7	—
9:23	4,700	4.87	—	17.5	26	—	67	—	7	—

The postoperative course was complicated by nausea and vomiting, but within 10 days these symptoms had disappeared. Improvement of strength was observed, associated with a marked improvement of appetite and a subsequent gain of 15 pounds (about 7 kg.). The results of blood studies made postoperatively are given in table 2. The ulcerative skin lesions above the metacarpal and metatarsal joints appeared to be healing within 10 days after splenectomy and by the fourth postoperative week the regions of ulceration were completely healed. The ulcerative lesion observed in the mouth was likewise healed.

Five months after splenectomy the patient was observed to have experienced continued improvement of strength and well-being. In addition to the gain of strength and weight there has been no evidence of local or systemic infection. The arthritic pain and swelling that had been observed preoperatively were considerably less severe during the postoperative period of observation. This improvement has continued during the subsequent five months. The patient's activity has been increased greatly in this period. Sternal aspiration was again performed on June 15, 1948. The examination of the marrow revealed it to be normally active. Active erythropoiesis was of the normoplastic type. Myelopoiesis appeared essentially normal. Megakaryocytes were not seen in the preparations examined, but platelet distribution was adequate. At the time of this report continued improvement of the patient's well-being and of his resistance to infection has been sustained.

Comment

The case presented revealed the classic features of Felty's syndrome, including advanced atrophic arthritis, splenomegaly, anemia and neutropenia. Splenectomy was performed in view of the marked neutropenia, fatigue, exhaustion and ulcerative lesions of the skin and mucous membranes, which were resistant to treatment. In the six months since the operation the patient has shown continued improvement, manifested by increased strength, gain of weight and maintenance of normal erythrocyte counts. There was improvement of the leukocyte counts after splenectomy. Preoperatively, leukocytes averaged about 1,900 per cubic millimeter of blood for 14 counts. Postoperatively, leukocytes averaged about 4,100 per cubic millimeter of blood for 26 counts. Improvement of the polymorphonuclear differential blood count was not as marked as that of the total leukocyte count. In some of the differential blood counts made postoperatively, low levels for polymorphonuclear leukocytes were obtained. These findings in postoperative blood studies closely paralleled those observed in the case reported by Zimmer.

Eosinophilia, which was not adequately explained, was observed preoperatively and postoperatively, in the case reported in which atrophic arthritis, splenomegaly and neutropenia were treated by splenectomy. Differential blood count studies revealed the highest per cent of eosinophiles to be 15 per 100 leukocytes in the preoperative counts, while postoperatively the highest eosinophilic leukocyte count was 14 per 100 leukocytes. Eosinophile counts ranging up to 13 per cent were present in one of the original cases reported by Felty (case 4), and eosinophilia was subsequently observed in the cases recorded by Craven and Zimmer. It is probable that the eosinophilia observed in this case represents a part of the syndrome including atrophic arthritis, splenomegaly and neutropenia.

In the majority of the cases of Felty's syndrome the bone marrow has been recorded as hyperplastic. Notable exceptions to this have been the case of Williams [23] studied at necropsy and the case of Felty's syndrome reported by Zimmer, in which the condition was treated by splenectomy. In the case reported by Williams there was diminution of granulopoiesis in bone marrow preparations. In the case recorded by Zimmer, maturation arrest in granulocytopoiesis was observed before splenectomy and this arrest in leukopoiesis disappeared after splenectomy. The case reported herein was characterized by a hypoplastic sternal bone marrow prior to splenectomy, and a normal sternal marrow five

months after splenectomy. Steinberg has expressed the opinion that if inactivity is present in the bone marrow splenectomy could not possibly be of value. Certainly this would be the case if the phagocytic hypothesis proved to be correct. However, if the humoral hypothesis of hypersplenism is correct, one might expect improvement in neutropenia after splenectomy in cases with maturation arrest of granulocytopoiesis or hypoplastic bone marrow, which is the result of humoral factors formed in the enlarged spleen. The case reported by Zimmer, and the case of Felty's syndrome reported herein, offer evidence in favor of the humoral hypothesis of hypersplenism, as observed in the syndrome of atrophic arthritis, splenomegaly and neutropenia.

In reported cases of primary splenic neutropenia the bone marrow has been recorded as hyperplastic [17, 19] or normal.[18, 20] In the case reported by Moore and Bierbaum,[24] the sternal marrow appeared more cellular after splenectomy than it was before. The authors considered the existence of a substance termed a "leukolysin," which was formed in the spleen and suppressed leukopoiesis in the bone marrow. It was previously stated by Rogers and Hall that the formation of a leukolysin in primary splenic neutropenia had not been disproved.

In the case under discussion, no definite conclusions can be reached as to the relative importance of the humoral and phagocytic hypotheses for the neutropenia encountered in Felty's syndrome. In this case the elevated leukocyte count in the splenic artery at the time of the operation is in favor of destruction of polymorphonuclear leukocytes in the spleen. However, the presence of a hypoplastic bone marrow before removal of a moderately enlarged spleen, with the bone marrow becoming normal in the examination made postoperatively, seems to be more consistent with the humoral hypothesis. The absence of phagocytosis of polymorphonuclear leukocytes in fixed sections of the spleen is also in accord with this latter hypothesis. In this case the evidence seems to be consistent with the opinion of Hirschboeck, who stated that in hypersplenism the answer to the problem may eventually be found in a combination of the humoral hypothesis and the phagocytic hypothesis. In the case reported, the evidence suggests that splenectomy may be of benefit to patients who have Felty's syndrome, even though the sternal marrow is not hyperplastic. This operation may be of value in Felty's syndrome with a hypoplastic bone marrow, provided there is no evidence of leukemia or infiltration of the marrow by tumor cells.

Summary

A case of Felty's syndrome with advanced atrophic arthritis, splenomegaly, anemia and neutropenia treated by splenectomy is reported. The sternal bone marrow before splenectomy was hypoplastic. Improvement of the patient's condition and improvement of the total leukocyte counts were observed postoperatively. The sternal bone marrow was normal postoperatively. It is our opinion that this patient was benefited by splenectomy.

Addendum—March 30, 1950: The patient under discussion has been examined at regular intervals since October, 1948. He has continued to remain in good health. The most recent blood count, March 30, 1950, revealed erythrocytes 5,380,000 per cubic millimeter of blood; hemoglobin 16.5 grams per 100 c.c. of whole blood; leukocytes 4,900 per cubic millimeter of blood. The differential count revealed the neutrophiles to comprise 34 per cent; lymphocytes 62 per cent, and monocytes 4 per cent. There have been no subsequent infections, and no evidence of active rheumatic infection since this report was submitted in October, 1948.

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LIPEMIA RETINALIS AND XANTHOMA DIABETICORUM IN DIABETES MELLITUS *

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LIPEMIA retinalis is a rare complication of diabetes mellitus. Falls [1] stated in 1943 that only 61 cases of lipemia retinalis had been reported up to that time and that his case was the sixty-second. We wish to place on record an additional instance of this condition which was observed in a young white adult male who was admitted to Kennedy Veterans Administration Hospital in moderately severe diabetic acidosis and in whom both lipemia retinalis and skin lesions of xanthoma diabeticorum were observed.

This interesting combination of physical findings has been described and the theoretical considerations discussed by previous authors [1, 7, 10, 11] and will not be repeated here. Briefly, the term "lipemia retinalis" was first used by Heyl [2] in 1880 when he described the appearance of the ocular fundi in a 20 year old male who was treated for diabetes mellitus. Heyl believed that the appearance of the retina was due to the presence of fat in abnormal amounts in the serum of the blood. Subsequent investigators confirmed the ophthalmoscopic findings. The majority of instances of lipemia retinalis had been noted in young male diabetics whose disease was complicated by varying degrees of acidosis. However, a few cases were observed in other conditions. Thus, Wagener [3] in 1922 found this condition in a nine year old boy who received radium therapy for lymphatic leukemia. In 1936 Holt et al.[4] noted lipemia retinalis in an 11 year old girl and in her two and one-half year old brother. In both, the liver and spleen were enlarged, the serum was milky and the blood fats were 7 per cent and 3 per cent respectively. They believed that these two cases probably had a familial anomaly of lipid metabolism analogous to Gaucher's disease, Niemann-Pick's disease and xanthomatosis. Kauffman [5] in 1943 observed lipemia retinalis in a 25 year old colored non-diabetic male in whom a history of alcoholism since 1939 was obtained. Lepard [6] in 1944 reported a case of lipemia retinalis in a presumably non-diabetic six year old white boy in whom, however, evidences of disturbances in the carbohydrate and fat metabolism were noted, the exact nature of which was not determined.

The incidence of lipemia retinalis in diabetes is very low. Marble and Smith [7] found nine instances in 11,000 cases of diabetics. Of these nine, six were males and three were females. Parker and Culler [8] in 1930 reviewed all the 38 cases which they found described in the literature. In 35 of these cases the sex was given and of these, 30 or 86 per cent, were males. The average age of the patients was 25 years, the extremes being nine and 50 in the 35 cases in whom the age was recorded. All the cases with the exception of that one reported by Wagener had diabetes mellitus and of the 37 diabetics all except two showed evidences of acidosis.

* Received for publication October 16, 1947.
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The condition, therefore, as stated above, had been observed predominantly in young males who had diabetes mellitus and in whom varying degrees of acidosis were present.

The appearance of the ocular fundi is characteristic and once seen the picture will engrave itself upon one's memory. The entire fundus appears pale grayish-pink or salmon colored; a lavender tint may or may not be noted; the optic discs are pale and grayish. The arteries and veins can be differentiated only with great difficulty and they appear as more or less flattened grayish-white or cream colored streaks; at times yellowish-white stripes are seen to accompany them. The creamy appearance of the vessels is more pronounced toward the periphery of the fundus.

We had no opportunity to examine the ocular fundi histologically in this condition, but Duke-Elder [9] states that "pathological examinations have shown consistently that the retinal tissues are normal but in the vessels the plasma is loaded with fat which permeates the intervascular spaces."

The level of blood lipids at which lipemia retinalis is found to appear has been reported to vary considerably. In general, most writers believe that lipemia retinalis is apt to appear when the lipid content is 3.5 per cent and to disappear when it falls below 2.5 per cent.

Treatment of the diabetes mellitus with diets containing small amounts of fat, large amounts of carbohydrates and adequate amounts of insulin causes prompt disappearance of the ocular findings.

Case Report

A 21 year old white male was admitted to the hospital on April 2, 1947 stating that about seven months previously he developed increasing polyuria and polydipsia. He estimated that his daily intake of water was approximately three gallons. This was equalled by his urinary output. Four months prior to admission he developed great craving for sweets such as candy, syrup and cakes but, despite the fact that he consumed large quantities of these foods, he remained hungry most of the time and he lost 26 pounds in weight. At about the same time he began to complain of weakness and that his legs often felt as if they had gone "to sleep"; at times he felt "lifeless." Later, he developed blurred vision and pains in his abdomen and back, occurring usually after meals. Three weeks prior to admission he had an episode of abdominal pain accompanied by vomiting and weakness. He consulted his doctor who told him that he had diabetes and advised hospitalization.

On admission the patient was moderately dehydrated and emaciated, the skin and tongue were dry and he appeared lethargic. There were numerous discrete, hard nodular infiltrations distributed irregularly over the entire body surface; these lesions were most numerous over the extensor surfaces of both upper and lower extremities and varied in size from pin-point to 4 to 6 mm. in diameter; they were raised above the surface and were yellow or orange in color. Many of the lesions presented a central depression imparting an umbilicated appearance. In addition, there was an irregular orange yellow macular eruption over the lower lumbar and upper sacral regions and the palms of the hands appeared pale orange in color. There was rigidity of the abdominal wall; the liver was palpable two fingers below the costal margin and the edge of the spleen was also palpable. Ophthalmoscopic examination revealed a remarkable appearance of the ocular fundi. The entire fundus was pale grayish-pink in color, with a lavender tint; the optic discs were pale; the arteries and veins near the disc were grayish-pink in color and at the periphery creamy white; they were mod-

erately engorged and could be differentiated only with difficulty. There were no exudates or hemorrhages. The urine contained 4 plus sugar and gave a strong reaction for acetone and diacetic acid. The fasting blood sugar was 198 mg. per cent and the carbon dioxide combining power was 38.4 per cent by volume.

The subsequent laboratory data are summarized in the accompanying table. The aspirated blood in the syringe appeared salmon pink in color with a lavender tint. Upon standing in the test tube the blood assumed a creamy-white color almost in its entirety and only the clotted portion retained a reddish color (figure 1).

Course: The patient responded promptly to treatment. During the first 24 hours he received 2,000 c.c. of 5 per cent glucose in normal saline solution plus 100 units of regular insulin. His urine became free from acetone and diacetic acid but it continued to give 4 plus reaction for sugar. During the second day he was given 1,000 c.c. of 5 per cent glucose in normal saline solution, a diet consisting of proteins 100 gm., carbohydrates 250 gm. and fats 50 gm. plus one glass of orange juice, one glass

TABLE I

Date	Fasting Blood Sugar (mg. %)	Total Blood Cholesterol (mg. %)	Cholesterol Esters (mg. %)	Total Blood Lipids (gm. %)	Blood Chlorides (mg. %)	CO_2 (vol. %)	Total Serum Proteins (gm. %)	Albumin (gm. %)	Globulin (gm. %)	A/G Ratio	NPN (mg. %)	RBC (million)	WBC (thousand)	Polys (%)	Lymphs (%)	Eos. (%)	Hg. (gm. %)	Hematocrit (%)	Sed. Rate (mm. in 1 hour)	Prothrombin Time (% of normal)	Stool Examination
4/3	198	1330	1064	20.6	412	38.4	6.5	3.9	2.6	1.5		3.45	10.4	71	27	2					
4/7		1066										4.3	5.4	50	43	7	13.8	39	2		
4/8	266	720		2.9																	
4/11																				100	
4/13	158	592																			
4/14																					neg.
4/17	133	506	351																		
4/21	89	389	277																		
4/25	74	306			468						28										

of milk and 150 units of insulin. On the third day after admission the ocular fundi regained their normal appearance. The fat content of the patient's diet was gradually increased until he was stabilized on a diet consisting of proteins 100 gm., carbohydrates 325 gm. and fats 120 gm. The daily insulin requirement was met by 50 units of protamine zinc insulin mixed with 30 units of regular insulin administered before breakfast. The patient felt well and gained several pounds in weight. Most of the skin lesions disappeared or were undergoing involution at the time of his discharge from the hospital on April 25, 1947.

Comment: The creamy appearance and the high lipid content of the blood readily accounted for the extraordinary picture noted in the ocular fundi. The prompt disappearance of these phenomena upon the institution of proper therapy bespeaks of their transitory nature. The high degree of lipemia is indicative of the efforts of the organism to supply fat as fuel for its energy requirements when carbohydrates cannot be utilized for this purpose because of the lack of

insulin supply. The appearance of the retina is merely the visible manifestation of this process. The changes in the blood lipids responsible for the appearance of lipemia retinalis are not well understood. Some investigators are of the opinion that emulsification of blood lipids and a change in the vessel walls altering their permeability are necessary to give rise to this phenomenon. Boyd [10] investigated the lipid composition of "milky" blood serum in rabbits and humans. He concluded that the proportion of different lipids in the blood serum might have some influence and that the less phospholipid was present in the serum in proportion to the other lipids the more likely was the serum to be "milky."

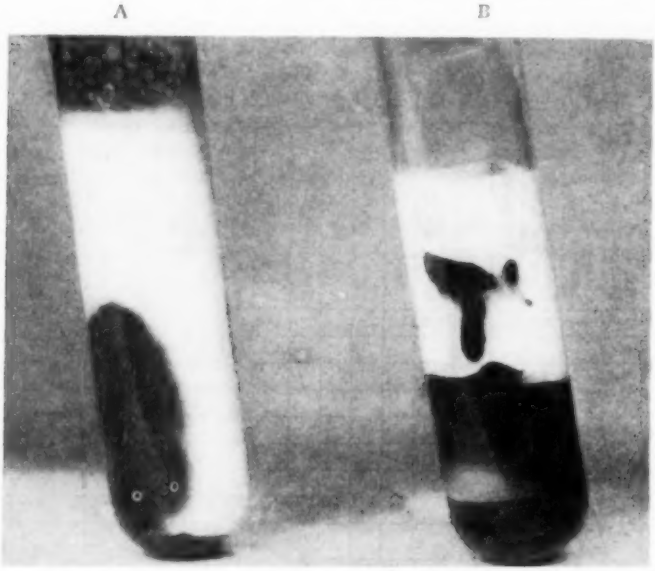

FIG. 1. A. Appearance of blood aspirated on the morning after admission. B. Appearance of blood aspirated one day later.

He was of the opinion that the phospholipids act as emulsifying agents and tend to permit colloidal solution of greater amounts of other fats such as neutral fats, cholesterol and cholesterol esters. It is probable that the presence of ketone bodies is at least partly responsible for this phenomenon since almost all reported cases occurred in diabetes with varying degrees of acidosis.

The pathogenesis of the xanthomatous skin lesions in diabetes mellitus has been the subject of considerable discussion. According to Sutton and Sutton [12] in diabetic xanthoma 90 per cent of the patients are males and 87 per cent are between the ages of 20 and 45 years. Wile et al.[13] studied the lipid content of these lesions; they found that cholesterol constituted only 16 per cent of the entire lipid content and only 2 per cent of the solid content of these lesions. They also found that xanthomatous lesions frequently occur in the absence of high

values of cholesterol in the blood and believed that the high cholesterol content of the blood in the lipemia of diabetes is an associated factor of the fat metabolism and not the primary cause of the xanthomatous lesions. Moore [14] states that diabetic xanthomas result in part from a deposit of cholesterol and other lipid substances in large mononuclear cells and in other instances represent the accumulation of similar lipids free in the tissues surrounded by masses of densely collagenous tissue.

In our case it appeared that the xanthomatous skin lesions were the result of the marked hyperlipemia and hypercholesterolemia; with the reduction of the blood lipids they promptly underwent involution and began to disappear.

Summary

A case of lipemia retinalis and lesions of xanthoma occurring in a young male diabetic is reported. Treatment of the diabetes with a diet high in carbohydrates and proteins and low in fats plus adequate amounts of insulin resulted in prompt disappearance of the lipemia retinalis and almost complete involution of the xanthomatous lesions.

Addendum: Follow-up examination on August 8, 1949 revealed the following: The patient felt well, had no complaints and worked as a full time farmer. In April of 1948 he developed "weak spells." He was treated in another hospital where his insulin dosage was reduced to PZI 20 units and regular insulin 35 units daily. Since then he felt well and his weight remained stable. Physical examination revealed normal conditions. The ocular fundi were normal and the skin was free of lesions. Fasting blood sugar was 75 mg. per cent, 1 hour postprandial blood sugar was 176 mg. per cent. Total serum lipids 840 mg. per cent, total serum cholesterol 210 mg. per cent and cholesterol esters 150 mg. per cent. Complete blood count showed red blood cells 5,300,000, hemoglobin 16.2 gm., white blood cells 7500, and normal differential.

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RECOVERY FROM ADDISON'S DISEASE DUE TO DIFFUSE VASCULAR DISEASE WITH SUBSEQUENT DEVELOPMENT OF HYPERTENSION AND GLOMERULONEPHRITIS *

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SINCE Addison's original description of the disease of the adrenal glands in 1855, a sufficient number of reports of this ailment have been recorded to indicate the etiologic factors which may be concerned. Tuberculosis of the suprarenal glands accounts for the great majority of cases, and atrophy of doubtful origin for most of the remainder. In the latter group, syphilis co-exists in a fair percentage. Amyloidosis, metastatic carcinoma, deep roentgen-ray therapy to the epigastrium,[1] mycosis fungoides, and lesions involving the semilunar ganglion, the solar plexus and the abdominal sympathetic chain [2] have been reported as causes. Toxins with special affinity for the adrenal cortex may produce necrosis followed by secondary atrophic changes.[3]

The following case is presented because it reveals a hitherto unreported cause for Addison's disease, the patient recovered and developed chronic hypertensive disease and glomerulonephritis, the underlying process involved many organs, and finally, because the findings furnish clinical confirmation of previous experimental studies dealing with the regenerative powers of the adrenal cortex and the adrenal medulla in man.

CASE REPORT

History. A white Jewish male began to suffer from intermittent claudication of the lower extremities in the autumn of 1934, at 19 years of age, and succumbed twelve and one-half years later to diffuse vascular disease of the adrenals, brain, heart, lungs, spleen and kidneys (figure 1).

His left great toe was amputated six months after the onset of symptoms. Following this operation, the circulation in all extremities appeared adequate, except that the right popliteal and posterior tibial arteries were closed. There was no pulsation in the left foot. Because of failure of the wound to heal, and on the basis of a diagnosis of thromboangiitis obliterans, the patient was treated with hypertonic saline intravenously. He had smoked 15 to 20 cigarettes daily, but stopped after the amputation.

In May 1935, he began to complain of weakness, easy fatigability, anorexia, vomiting and diarrhea, and developed striking pigmentation of the skin of the face, arms, legs and buccal mucosa. On admission to the Mount Sinai Hospital, in New York City, his urine showed a trace of albumin and a few hyaline casts. His weight, which had been 160 pounds (73 kg.) in December 1934, had dropped to 93 pounds (42 kg.) by August 1935. Intravenous hypertonic saline relieved his symptoms. His blood pressure fell to 80 mm. systolic, 46 mm. diastolic and a diagnosis of Addison's disease was made. At this time, one of us (L. G. R.), who saw the patient in consultation, felt that there was atrophy of the adrenals on a vascular basis. This patient was the subject of a case report by Dr. Samuel Silbert.[4] He failed to improve

* Received for publication March 6, 1948.

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with salt and Eschatin (a purified extract of bovine adrenal cortex containing about 25 dog units per cubic centimeter), but rallied promptly when the latter was replaced by Swingle's cortical extract. This improvement was interrupted during an upper respiratory tract infection in December 1935. Salt therapy was discontinued in 1938, and cortin in 1939. In the four years between 1935 and 1939, he had several attacks of acute catarrhal jaundice, associated with enlargement of the liver and spleen, clay-colored stools and bile in the urine.

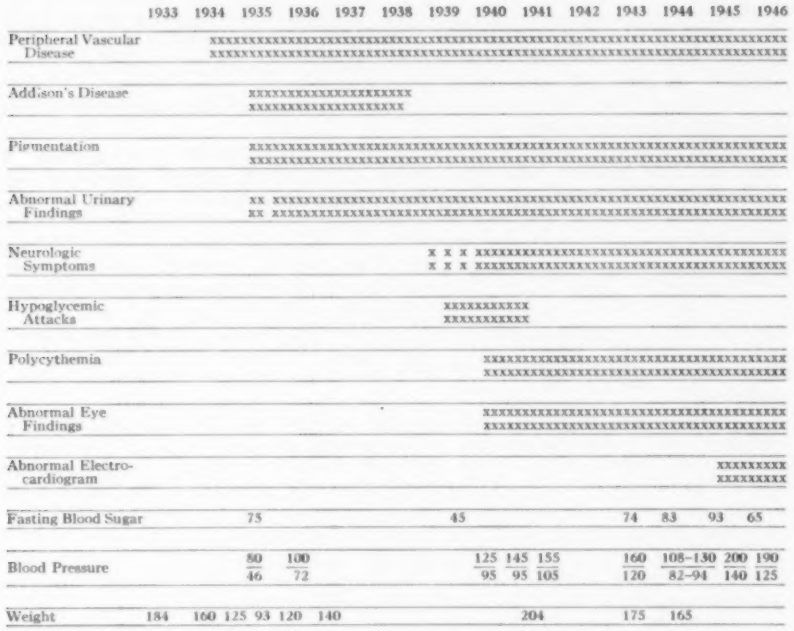

FIG. 1. Graphic summary of the clinical course of patient H. G.

In November 1939, he developed random, jerky movements of the upper extremities and tic-like movements of the face; his speech was unclear, and he became irritable and combative. He was admitted to the Mount Sinai Hospital for the sixth time, and during the subsequent three year period had a total of 19 admissions to that institution. In March 1940, he developed attacks of faintness, weakness and epigastric pain when he missed a meal. This was followed shortly by recurrent convulsive seizures, which were relieved by orange juice. One blood sugar was as low as 45 mg. per cent. During this period of hospitalization, the blood pressure was 125 mm. Hg systolic, 95 mm. diastolic. There were no cardiac abnormalities. A blood count revealed 17.5 gm. of hemoglobin, 6,070,000 erythrocytes, a hematocrit of 48.5, and an associated blood urea nitrogen of 21 mg. per cent. It was suggested that the polycythemia was a manifestation of hemoconcentration. Repeated urine examinations showed a slight amount of albumin in one specimen, but were otherwise normal. An electrocardiogram showed only left axis deviation. Sectional radiography of the adrenal areas revealed no masses, and the kidneys were normal in size, shape and posi-

tion. Roentgen-rays of the chest and skull were normal. The diagnoses which were considered at this time were Sydenham's chorea, Wilson's disease, vascular disease and/or hypoglycemia. In May 1940, he was given glucose and saline intravenously, additional salt by mouth, and daily intramuscular injections of 5 mg. of desoxycorticosterone. In addition, he was placed on a high caloric, high vitamin diet, containing 800 gm. of carbohydrate. The convulsions, choreiform movements and trismic speech disappeared. His blood pressure, however, rose to 150 mm. systolic, 105 mm. diastolic. At this time the desoxycorticosterone was replaced by Swingle's triple concentrate cortical extract (1 c.c. equals 200 gm. of fresh cortex), which was given in 1 c.c. doses twice daily. A glycine tolerance test and a thiamine tolerance test were both normal. Repeated neurologic examinations, performed by Dr. Israel Wechsler, were negative. In June 1940, a skin biopsy showed melanin pigment in the basal cell layer.

In August 1940, while on the regime outlined above, he was symptom-free, and could remain so without food.

In October 1940, however, anorexia and easy fatigability recurred during an attack of acute purulent right otitis media. Roentgen-ray showed changes in the structure of the right mastoid. The blood pressure was 160 mm. systolic, 110 mm. diastolic, and the retinal arteries were narrowed, with A–V compression. The urine had a trace of albumin, occasional red blood cells, and hyaline casts. During the next year, these findings progressed, and there were marked albuminuria and numerous formed elements. Only 30 per cent of administered phenolsulfonphthalein was excreted in three hours. A glucose tolerance test, which was prolonged to four and one-half hours, produced a hypoglycemic reaction, but results with this test at other times were variable. Studies of the sympathetic tone of the arteries, and measurements of the digitial and brachial blood pressures, revealed increased peripheral resistance.

The abnormal neurologic manifestations returned and the convulsive episodes continued with increasing severity and frequency, but they were associated with normal blood sugar levels. Visual field studies showed an inferior temporal defect, and funduscopic examination revealed an occlusion of a branch of the right retinal artery. Repeated study showed a widespread extension of this process. Evidences of mental deterioration appeared. A biopsy of skin and muscle from the left deltoid region showed fibrinoid degeneration and necrosis within arteries and arterioles, with variable degrees of vascular occlusion, and increased melanin pigment in the stratum germinativum of the skin. The muscle fibers were normal.

The patient's weight remained at approximately 205 pounds. In May 1941, during an attack of infectious hepatitis, urine examinations showed an ability to concentrate to 1.023, albumin varied from a trace to three plus, and there were occasional red blood cells, white blood cells and hyaline casts. In October 1942, the basal metabolic rate was minus 11 per cent, and 17-ketosteroid excretion was normal.

Because of the repeated convulsive seizures, the patient was given dilantin in 1943. The liver and spleen were easily palpable at this time. The blood pressure was 175 mm. systolic, 120 mm. diastolic, and the heart was thought to be slightly enlarged. He was given moccasin venom in an attempt to control the fundal hemorrhages.

The patient was admitted to Montefiore Hospital in September 1943, and remained here until his death. On admission, physical examination disclosed that the patient was rather obese, slightly drowsy, and that his memory was impaired. He did not appear acutely ill, however. The skin was slate-colored, and there were black freckles on the lips and buccal mucous membranes. Pigmentation was especially marked around the nipples, genitalia, buttocks, knees, elbows and ear lobes. There was a soft, localized systolic murmur at the apical area of the heart. The rhythm was regular. The blood pressure was 160 mm. systolic, 120 mm. diastolic. The liver,

spleen and kidneys were not palpable. There was a small, superficial ulceration on the anterior aspect of the scrotum, and a second shallow ulcer about 2 cm. in diameter over the left medial malleolus. The dorsalis pedis pulsation was good on the right, but feeble on the left. Posterior tibial pulsations were not obtainable. No pulsation was elicited in the left popliteal artery. There was marked weakness in the left arm, which developed a fine, rapid tremor on exertion. All deep reflexes were hyperactive, but there was no ankle clonus or positive Babinski. (On examination one month later, the latter was positive on the left.)

The urine on this admission showed a heavy trace of albumin, numerous red blood cells, a few white blood cells and occasional granular and hyaline casts. On concentration test, the specific gravity was fixed at 1.012. Urea clearances were 48 and 50 per cent. The hemoglobin was 12.5 gm., erythrocytes 4,500,000, leukocytes 9,600, with 69 per cent polymorphonuclears of which 7 per cent were band forms, 23 per cent lymphocytes, 6 per cent monocytes and 6 per cent eosinophiles. The erythrocyte sedimentation rate (Cutler method) was 28 mm. in one hour. The fasting blood sugar was 74 mg. per cent, urea nitrogen 17.0 mg. per cent, chlorides 361 mg. per cent, sodium 323 mg. per cent, potassium 18.0 mg. per cent, carbon dioxide combining power 55.2 volumes per cent, cholesterol 347 mg. per cent, creatinine 1.5 mg. per cent, calcium 10.1 mg. per cent, phosphorus 4.1 mg. per cent, and the total protein was 7.9 gm. per cent with 5.6 gm. of albumin and 2.3 gm. of globulin. Blood Wassermann and Kahn tests were negative. Two glucose tolerance tests were normal. Chest x-ray showed a generalized increase in density over the hilar portion of the right lung field. The electrocardiogram, as before, showed only left axis deviation. Fluoroscopic examination revealed a small heart. A retrograde pyelogram was normal. Spinal fluid examinations, including manometric determinations, were not unusual. An electroencephalogram showed grossly abnormal waves. Fasting blood sugar levels and tolerance tests, and blood sugars determined repeatedly during convulsions, were normal. Ophthalmoscopic examination revealed many vitreous opacities and retinitis proliferans with retinal detachment in the right eye. The arteries were markedly attenuated and many newly-formed vessels were seen. The left fundus resembled the right, except for the absence of retinal detachment.

The diagnosis at this time was diffuse vascular disease, with involvement of the arteries of the lower extremities, brain, adrenals and kidneys. At this time, it was felt that a glomerular lesion was probably present because of the microscopic hematuria and the marked diminution of renal function.

The patient continued to display neurologic disturbances, which were characterized by mental torpor and emotional instability. His speech was dysarthric, and there was spontaneous laughing and crying. His gait became extremely unsteady, and retropulsion was marked. In September 1945, physical examination revealed, in addition to the findings on admission, that the skin and subcutaneous tissue felt thicker than normal. There was suggestive clubbing and spading of the finger-tips, with brownish pigmentation in the supra-ungual areas. The nail-beds were moderately cyanotic. At this time, a Babinski sign was elicited on the right, and there was increased flexor tone in the right upper extremity.

Hematologic studies, which were done by Dr. Michael Rubinstein, showed 17.3 gm. of hemoglobin, 5,480,000 erythrocytes, 11,500 leukocytes consisting of 80 per cent polymorphonuclears, of which 4 per cent were band forms, 12 per cent lymphocytes, 6 per cent mononuclears and 2 per cent eosinophiles. There were 480,000 platelets, and the hematocrit (Wintrobe method) was 48 per cent. The total plasma volume was increased to 58 c.c. per kg.; the total blood volume (Evan's blue) was 115 c.c. per kg. The mean corpuscular volume was 87.5 cubic microns, coagulation time 10 minutes, bleeding time 2 minutes, clot retraction time normal, tourniquet test negative, and the erythrocyte sedimentation rate (Cutler tube) was 0.5 mm. in one hour. The

sternal marrow was very cellular, with a marked increase in the red cell series and a moderate increase in the number of megakaryocytes; the total nucleated cell count was 185,000, with 110 megakaryocytes per cu. mm. The differential count was 2 per cent myeloblasts, 5 per cent promyelocytes, 18 per cent neutrophilic myelocytes, 1.5 per cent eosinophilic myelocytes, 20 per cent non-segmented neutrophiles, 15 per cent segmented neutrophiles, 0.5 per cent eosinophiles, 5 per cent lymphocytes, 6 per cent erythroblasts, and 28 per cent normoblasts.

Roentgenograms of the paranasal sinuses showed no abnormalities.

In November 1945, the patient developed bloody expectoration and jaundice. A roentgenogram of the chest revealed a triangular shadow of density in the right mid-lung field. The electrocardiogram showed upright QRS complexes in Leads I and II, and an inverted QRS in Lead III. The ST segment in Lead I was depressed and the T wave was small. The ST segment was depressed in Lead CF_5 and the T wave was inverted. The QRS contours in all of the chest leads were normal, however. These findings, when compared with earlier records were interpreted as evidence of increase in active mass of the left side of the heart.

FIG. 2. Adrenal glands. Note the extensive scarring and nodular appearance of the gland substance. The right adrenal is the larger.

He recovered from this episode in one week, but the downward course continued. The convulsive seizures recurred frequently, and he developed progressive urinary and fecal incontinence and died on November 10, 1946, during an illness characterized by fever, cyanosis and stupor which lasted one week. An x-ray of the chest, which was taken 48 hours before death, showed a diffuse, non-homogeneous infiltration extending from the left lung-root, in a fan-like fashion, into the upper lung field. An irregular area of decreased density overlay the anterior portion of the second rib. The right lung showed some increase in vascular density, involving particularly the larger vessels. A few patches of poorly circumscribed, soft infiltrations were seen in the first and second interspaces in the right mid-lung field.

Necropsy Findings. The *lungs* were heavy. The middle two-thirds of the left lung was non-crepitant. On section, this zone presented a smooth surface, and was rubbery and vaguely nodular. There were similar scattered foci in the right lung; some measured up to 3 cm. in diameter. A few small hemorrhages were noted in both lungs. A superficial patch of atelectasis was found in the lower medial portion of the right lower lobe. The bronchi, lymph nodes and major vessels were normal.

The *heart* weighed 410 gm.; the left ventricle was hypertrophied. The muscle was firm, red-brown, and showed numerous yellow-gray streaks. The auricular surface of the mitral valve, along the line of closure, had a row of friable, warty, gray vegetations, measuring up to 3 mm. in thickness. Otherwise, the valve appeared normal. The ostium and proximal portion of the right coronary artery were completely occluded for a distance of 1.5 cm. by an adherent red thrombus. The walls of the proximal portions of both main coronary arteries were thickened by atherosclerotic plaques. The remainders of the right and left coronary arteries were widely patent. The abdominal portion of the aorta showed several atheromatous deposits, between which the intima was wrinkled longitudinally. The large venous trunks were not unusual.

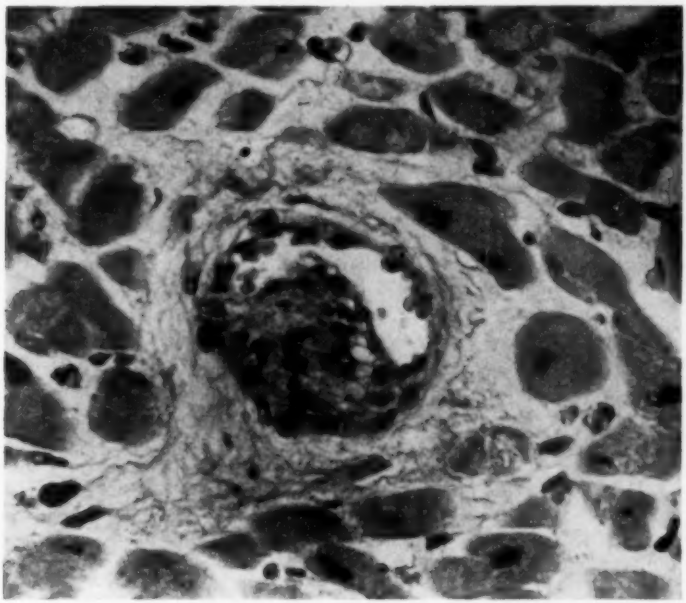

FIG. 3. Myocardium. A small vessel showing marked intimal proliferation with narrowing of the lumen.

The *liver* was moderately enlarged (2,160 gm.), but otherwise appeared normal.

The *spleen* was considerably enlarged (420 gm.). Its capsule was thickened. The surface revealed several deep scars, which on section were seen to represent old infarcts. At one pole, there was a recent infarct measuring 2 cm. in diameter. The cut surface was dark red and contained numerous large follicles.

The *adrenals* were greatly shrunken and were embedded in a large amount of fat (figure 2). The right weighed 2.9 gm., and the left 1.6 gm. These organs were flat, irregularly nodular, and were traversed by many broad scars. On section, the parenchyma was uniformly gray-brown and was distributed as nodules which were separated by broad bands of fibrous tissue. No distinction between cortex and medulla was apparent.

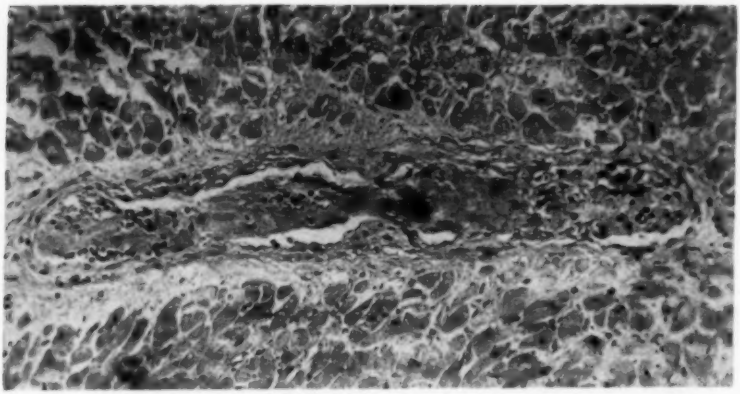

FIG. 4. Myocardium. A thrombus in a venule. Note proliferation of the intima at one end of the section.

Each kidney weighed 150 gm. The capsules were stripped with considerable difficulty, and revealed coarsely granular, mottled gray and pink surfaces on which a few small cysts were seen. The cortex was slightly narrow and pale brown in color. Cortical markings and cortico-medullary junctions were obscured. In the medulla, and extending for a short distance into the cortex, there were numerous

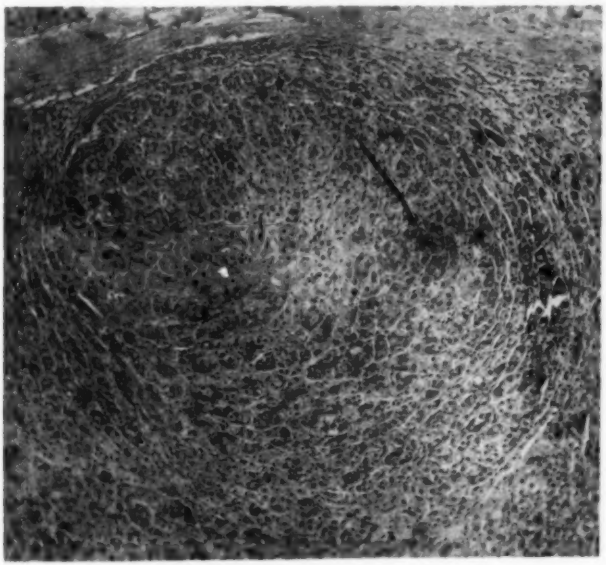

FIG. 5. Adrenal gland showing nodular arrangement of the cortical cells.

chalky, golden-yellow, tiny streaks and specks. The pelves, ureters and larger vessels appeared normal.

The *brain* was extensively atrophied and contained many cortical patches of old and recent encephalomalacia. The smaller pial vessels had thickened walls, and some appeared to be occluded. The larger vessels at the base seemed to be normal.

The *pituitary* gland weighed 530 mg. and was not unusual.

Microscopic Examination: The *cardiac* muscle fibers were considerably hypertrophied. There was extensive patchy, fibrous replacement of the muscle, especially in the left ventricle. Focal infiltration by lymphocytes and plasma cells and occasionally by polymorphonuclear cells, was present in perivascular zones. *Many endothelial-lined spaces, apparently capillaries, arterioles and venules, showed proliferation and*

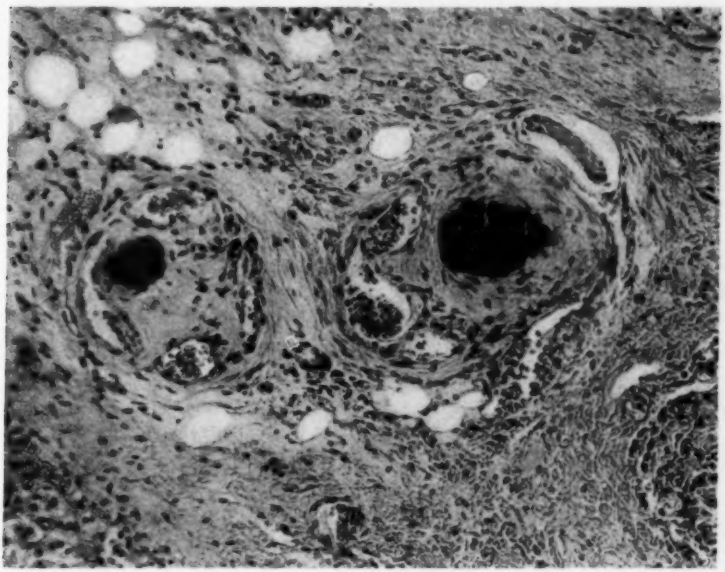

FIG. 6. Adrenal gland showing vessels whose original lumens have been obliterated by organized thrombi in which calcium salts have been deposited. Note the recanalized channels.

swelling of the endothelium (figures 3 and 4). In some, the proliferated endothelium grew into and occasionally occluded the lumen. Other channels contained hyaline thrombi which frequently occluded them. The lumen of the right *coronary* artery was completely obstructed by a recent thrombus which was superimposed on a well organized one. There was moderate subintimal thickening of this vessel, with numerous foam cells, a moderate number of capillaries, and several focal hemorrhages. There were also present subintimal infiltrations of small lymphocytes. The media contained a large number of capillaries and was focally infiltrated by a moderate number of lymphocytes. Similar cells, as well as proliferating capillaries, were found in the adventitia. The mitral leaflet contained a moderate number of thin-walled

FIG. 7. Kidney. Marked changes in the normal architecture of all the elements in the cortex.

blood vessels. Along its auricular surface there was an organizing mural thrombus, without bacteria or cellular reaction.

The subintima of the *aorta* was thickened by collections of foam cells and hyaline plaques; there were also a few focal collections of lymphocytes and capillaries. Lymphocytes were present in the media, which contained some fibrous scars running in the same direction as the muscle fibers. A moderate number of capillaries was present. The adventitia was diffusely infiltrated by lymphocytes.

The *pleura* over most of the lungs was thickened, congested and contained lymphocytes. The *parenchyma* showed patchy atelectasis. The interalveolar septa were markedly thickened by fibrous tissue. Many of the alveoli were filled with macrophages, lymphocytes and polymorphonuclear cells. Some contained fibrin which, in places, was pressed against the interalveolar septa, giving the appearance of a hyaline membrane. In places, the fibrin was undergoing organization. The bronchial walls and lumens were frequently infiltrated by polymorphonuclear cells, lymphocytes and macrophages. The blood vessels showed changes similar to those described in the heart.

There was nothing remarkable in the *liver* parenchyma or its blood vessels.

The *spleen* contained many large corpuscles, with prominent germinal centers. The pulp and sinuses were congested. The small arteries and arterioles showed hyaline sclerosis. A recent infarct was noted, which resulted from the occlusion of a medium-sized artery. There was endothelial proliferation, and a thrombus was in process of organization in this vessel.

In the *pancreas*, a few small blood vessels were occluded by canalized thrombi. The arterioles had hyalinized and thickened walls.

There were large lymph follicles with prominent germinal centers in the ileum. The *mesenteric* arterioles had thick walls, but otherwise appeared normal.

Many microscopic sections of both *adrenals* were studied, revealing *complete distortion of the normal architecture*. Each gland was composed of nodules of cortical tissue, varying considerably in size and shape (figure 5). Some were partly, and others completely enclosed in a fibrous capsule of varied thickness. In places, the fibrous capsule continued as thick bands through the adrenals, with nodules of cortical tissue arranged in linear fashion along their sides. In areas where the nodules of cortical cells were not encapsulated, they tended to streak irregularly into the fat. In some areas, masses and branching cords of non-encapsulated cortical cells lay in the adipose tissue with collections among them of lymphocytes, plasma cells and macrophages containing old blood pigment. The cortical nodules consisted of branching cords of extremely large cells without definite zonal arrangement. The lipoid content varied considerably, although, in general, it was very poor. There were scattered islands of large foam cells, and occasional bizarre cells with large, hyperchromatic nuclei. Many cells contained yellow metabolic pigment. Small scattered foci of calcification were found in the cortex. *No medulla was present in any of the sections. Many of the small arteries and arterioles showed changes similar to those described previously; they were partly or completely occluded by cellular masses resembling organized thrombi. Other small vessels contained multiple lumens, separated by fibrous septa, in which calcium deposits were occasionally seen* (*figure 6*).

The *kidneys* showed marked and widespread alterations in the parenchyma and the stroma (figure 7). About one-half of the glomeruli were shrunken and fibrotic, or hyalinized. The remainder were enlarged, bloodless and quite cellular (figure 8). A few, however, were engorged. Many of these showed hypertrophy and hyperplasia of the epithelium of Bowman's capsule and of the tufts, but there were only a few suggestive cellular crescents. Fibrous thickening of Bowman's capsule and thickening of the glomerular basement membrane was more common. A considerable number showed adhesions between the glomerular loops and Bowman's capsule (figure 9). There were very few glomeruli which approached a normal appearance.

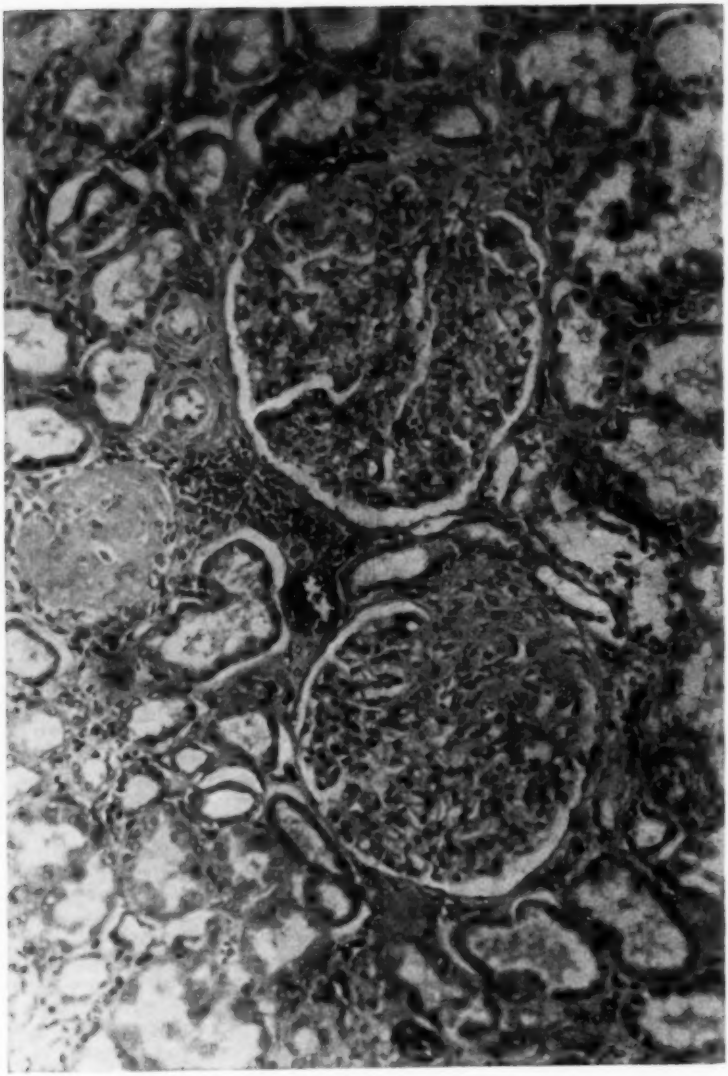

FIG. 8. Kidney. Cortex showing large size, marked cellularity and anemia of glomeruli and proliferative thickening of arterioles.

The large arteries showed a moderate degree of intimal proliferation and fibrosis, with thickening and reduplication of the elastica. The smaller arteries and arterioles showed more marked proliferative thickening and edema, with narrowing of lumen, which was frequently extreme. Although hyaline sclerosis of arterioles was seen only occasionally, it was marked. ***Many kidney sections were studied, but no occlusive vascular lesions, of the type described in other organs, were found.***

The tubules showed marked atrophy. The remainder were hypertrophied and dilated, and the epithelium was vacuolated and frayed. The lumens contained much granular debris, hyaline casts, and a few polymorphonuclear and epithelial cells. There was a fairly diffuse and marked increase in connective tissue stroma, with marked focal, and slightly diffuse infiltration of lymphocytes and plasma cells.

Medial sclerosis was noted in the small arteries and arterioles of the *bladder* and *prostate*. The *testes* appeared normal.

The *thymus* consisted of large, plump reticulum cells and lymphocytes.

The *thyroid* gland showed an increase in connective tissue. This created nodules in some of which the glandular elements were atrophied. In other nodules, the follicles were filled with well-stained colloid. The connective tissue stroma, and especially the nodules containing atrophic glandular elements, were densely infiltrated with lymphocytes and plasma cells. The small arteries showed the same changes described in the heart.

The *parathyroid* glands contained approximately equal numbers of small, dark, and large, pale chief cells. Oxyphil cells were rarely seen.

There were no significant changes in the *pituitary* and *pineal* glands.

The only changes noted in the *lymph nodes* were unusually large follicles and prominent germinal centers.

The *skin* contained numerous chromatophores with brown pigment in the basal layer of the epidermis and in the superficial layer of the dermis.

There were patchy areas of softening in the *brain*. The cortex had a spongy appearance, the ganglion cells had disappeared, and the underlying white matter contained a concentration of oligodendroglia. A linear cortical scar, densely infiltrated with lymphocytes, was present. The walls of the arterioles were thickened and quite cellular. A few small arteries in the pia and parenchyma showed the same changes as many of the blood vessels in the heart. One small artery contained several recanalized channels, which were completely occluded by fibrinoid material. The *spinal cord* was not remarkable. The small arteries and arterioles showed hyaline thickening of the media.

Anatomical diagnoses were amputation of the first toe of the left foot for gangrene; hypertension (clinical); generalized obliterative angiitis; subacute and chronic glomerulonephritis; extensive fibrosis with marked cortical regeneration of the suprarenal glands and absence of the medulla (probable old infarction); multiple regions of softening of the brain; pigmentation of the lips, external genitalia, skin, nipples and buccal mucosa; atrophy and fibrosis of the thyroid with marked lymphocytic infiltration and adenoma formation; subinvolution of the thymus; hypertrophy and dilatation of the left ventricle; patchy myocardial fibrosis of the left ventricle; organizing nonbacterial thrombotic endocarditis of the mitral valve; multiple old and recent infarcts of the spleen; chronic splenitis with splenomegaly; acute and chronic pneumonitis; acute and chronic bronchitis; chronic lymphadenitis of the abdominal lymph nodes; and decubitus ulcer of the sacrum.

Discussion

We believe that the case herein reported demonstrates a previously unrecorded etiology for Addison's disease; namely, a generalized obliterative angiitis with involvement of the adrenal vasculature. (This case was very briefly described in a larger series of patients with Addison's disease to emphasize length

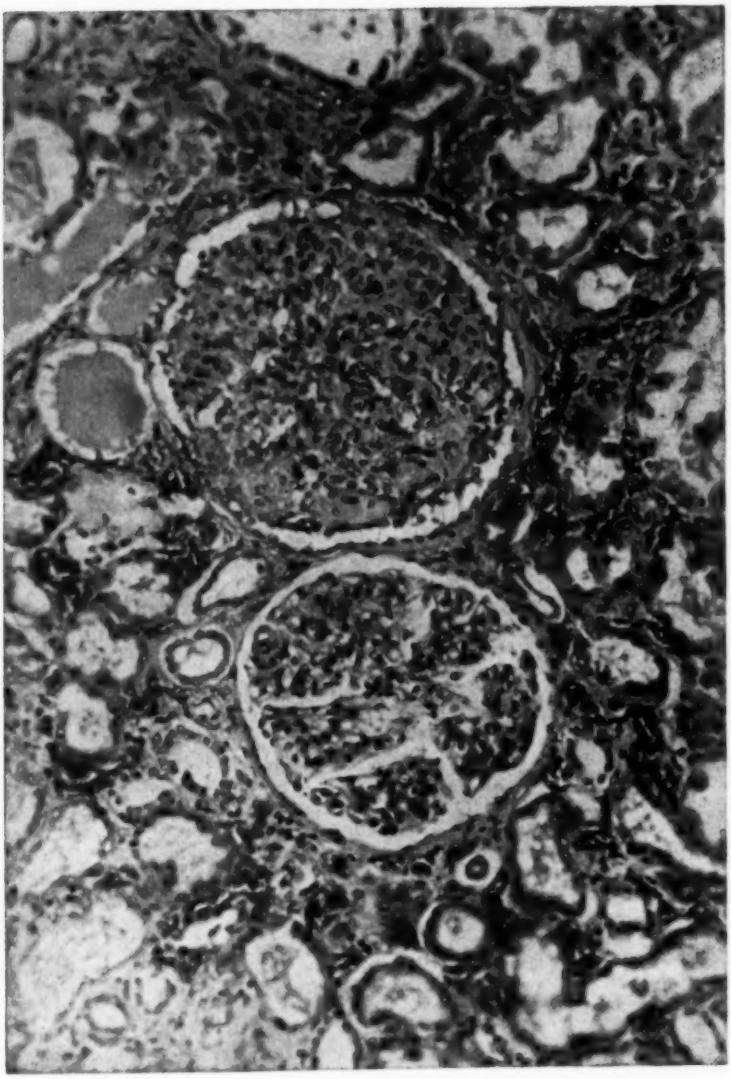

FIG. 9. Kidney. Note proliferation of glomerular epithelium and adhesions to Bowman's capsule.

of survival while under treatment with Swingle's adrenal cortical extract.[5]) It may be argued that the picture should properly be termed chronic adrenal insufficiency, because only a single instance of Addison's disease with recovery has previously been recorded.[6] *

The fact that our patient was able to survive for eight years after cortical extract and salt therapy had been discontinued, merely emphasizes the unusual etiology. The usual agents concerned in the production of Addison's disease may be described as processes which either replace the entire adrenal cortex (tuberculosis, neoplasm), or exert toxic effects which influence each adrenal cortical cell. The prognosis in this patient was governed by the distribution and tempo of the occlusive vascular process in the suprarenals. It is noteworthy that the adrenal medulla was completely absent in this patient at necropsy. In this connection, it should be pointed out that experimentally, if the blood supply to the adrenal is cut off for a period of 24 hours, cortical tissue will regenerate, whereas the medulla disappears permanently.[7, 8] The numerous areas of hyperplasia of the cortex, which were demonstrated at necropsy, give ample proof of the regenerative powers of the suprarenal cortex of this patient, and indicate the patchy character of the vascular involvement of these glands. Fortunately, a sufficient number of blood vessels remained open to permit regeneration.

The neurologic disturbances are adequately explained by the occurrence of numerous thrombotic episodes, with multiple scar formation, which were probably chiefly the result of the diffuse arteritis in the brain. The rôle which the erythremia may have played in the production of the thromboses must remain conjectural. The periods of hypoglycemia which occurred after the picture of Addison's disease had subsided are more difficult to understand. However, the diffuse vascular process in the brain and pancreas may have been factors. The last attack of acute catarrhal jaundice preceded the onset of hypoglycemia by a considerable interval, and is therefore an unlikely cause for the latter. The eye findings, which included retinal hemorrhages, retinitis proliferans, detachment of the retina, vitreous opacities and blindness, were all secondary to the local occurrence of the generalized vasculitis. Neither cardiac enlargement nor congestive heart failure was evident clinically, although in the last year of the patient's

* The latter is the case of a 26 year old man who presented himself at the Mayo Clinic in August 1922, complaining of pigmented skin and weakness of nine months' duration. A few months before these symptoms had appeared, he had been seized with severe abdominal pain, followed by hematemesis and melena, for which he had been kept in bed on a peptic ulcer regime for eight weeks. The pigmentation on the face and neck gradually became darker, and then involved the genital, anal and nipple regions, and points of friction. The pigmentation was adversely affected by exercise, and he had suffered five attacks of pain in the left lumbar region. He had lost 39 pounds during the nine months of illness and suffered occasional periods of nausea and vomiting. His blood pressure was 94 mm. systolic, 60 mm. diastolic, and the basal metabolic rate was − 10 per cent. X-rays of the chest and stomach were normal. A diagnosis of Addison's disease was made, with the concurrence of two consulting dermatologists.

The patient gained 20 pounds and his blood pressure rose to 130 mm. systolic, 80 mm. diastolic, after starting treatment with epinephrin, salt, and desiccated whole gland. His strength returned slowly and the pigmentation decreased. Four years later, on the same medication, his blood pressure was normal and his color good. By October 1928, the pigmentation had almost completely disappeared. When last heard from in 1939, 17 years after the onset of his illness, the patient was in excellent health. His blood pressure at that time was 120 mm. systolic, 80 mm. diastolic, and he weighed 165 pounds (when first seen, his weight was 129 pounds). There were only slight evidences of pigmentation. No evidence of tuberculosis was ever found, and the assumption was that the injury to the suprarenals was of a functional nature.

life electrocardiograms gave evidence of an increase in mass of the left ventricle. The coronary thrombosis was not suspected during life, and there was no clue to the local vasculitis.

The pigmentation was the only clinical manifestation which persisted throughout the course of the Addison's disease, and it remained unmistakably Addisonian in character until the end.*

One of us (L. G. R.) has observed a previously hypertensive female, who, four hours before death due to Addison's disease, had a systolic blood pressure of 160 mm. In our patient, however, there is no reason to believe that Addison's disease was present for the last eight years of his life. Chronic hypertension developed during the period which followed the subsidence of the Addison's disease. In this connection, it should be pointed out that the kidneys at necropsy were the subject of much discussion. There was a group who felt that the pathological findings were those of chronic glomerulonephritis, and that the hypertension could be explained on this basis. Another competent observer was of the opinion that the appearance of the sections was entirely consistent with that of advanced arteriolar nephrosclerosis. It is clear, however, that the vascular lesions which were evident in other organs were not present in the kidneys. The fact that, clinically, abnormal urinary findings, including microscopic hematuria, were evident long before the appearance of hypertension, when the patient was only 21 years old, would favor the diagnosis of glomerulonephritis.

Summary

A case of recovery from Addison's disease, with subsequent development of chronic hypertensive disease is herein reported. The etiology of the disease of the suprarenal glands was an obliterative angiitis, which resulted in infarction of these organs, with subsequent regeneration of adrenal cortical tissue, but permanent loss of adrenal medulla. The obliterative angiitis was generalized and involved many other organs, including the brain, heart, lungs and spleen. The hypertension was probably related to a concomitant chronic glomerulonephritis.

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* Dr. Harry Keil, dermatologist, felt that the skin lesion was a manifestation of juvenile acanthosis nigricans, but Dr. Samuel H. Rosen, pathologist, was of the opinion that the skin biopsies did not warrant this diagnosis.

CHLOROMYCETIN IN THE TREATMENT OF TYPHOID FEVER *

By LEIF Y. JACOBSEN, *Douglaston, L. I., N. Y.*, and RICHARD A. BRODERICK, *Bayside, N. Y.*

NOT many reports on the treatment of typhoid fever with chloromycetin have been published. Since typhoid fever has become a rare disease in the United States, the opportunity for using this new antibiotic has not often presented itself. The most extensive study published to date was on 10 cases of typhoid fever occurring on the Malayan peninsula and reported by Woodward et al.[1] The New England Journal of Medicine in an editorial in the May 1949 issue, summarizes the knowledge of the antibiotic up to that date.

A case of typhoid fever was admitted to the Flushing Hospital and treated with chloromycetin. Some new light may be gathered from this case and other previous knowledge may be reëmphasized.

CASE REPORT

A 14 year old Negro male was admitted to the Medical Service of the Flushing Hospital on April 28, 1949, with a five day history of sore throat, fever, headache, and malaise. The patient had been treated for two days with sulfadiazine as an out-patient for his sore throat.

Past history, family history and systemic review were essentially negative. On admission temperature was 103.6° F., pulse 100, respirations 20, blood pressure 108 mm. Hg systolic and 60 diastolic. Positive physical findings included: dry coated tongue, slight trismus, inflamed nasopharynx, occasional musical râles and wheezes scattered over both lung fields; no palpable liver or spleen, no rash.

On admission the blood count showed: white blood cells 9,100 with 65 per cent polynuclears, 5 per cent stabs, 30 per cent lymphs; red blood cells 4.27 million with 12.2 gm. hemoglobin. Urine negative, no sickling of red blood cells, heterophile titer negative on two occasions, roentgen-ray of chest negative.

Penicillin was started on admission after blood and throat cultures were taken, but this was discontinued after three days when temperature persisted around 104° F. and follow-up white blood cell counts ranged between 2800 and 5800.

Blood culture was positive for *S. typhosa* seven days after admission (12 days after onset of illness). Agglutination tests with the patient's serum were positive on the eleventh day of illness 1:640 for Typhoid "H" and 1:320 for Typhoid "C."

Chloromycetin was begun on the twelfth day of illness. Dose: 500 mg. initial dose, 250 mg. every two hours for eight days, then 250 mg. every four hours for two more days. (By mistake the recommended dose of 50 mg./kg. as the initial dose was not given.) Supplemental treatment consisted of 3000 c.c. intravenous fluids and parenteral vitamins daily. Later hematinics were added because the red blood cell count had dropped to 3.1 million.

Temperature reached normal after seven days of chloromycetin therapy. After 17 days of normal temperature, and 12 days after chloromycetin was stopped, temperature began to rise and went as high as 106° F. Two blood cultures were again positive for *S. typhosa*. Treatment with chloromycetin was reinstituted: 250 mg. every hour until 50 mg./kg. had been given (dosage had to be divided at first because of extreme nausea), then 250 mg. every two hours. On the fifth day of the second course of chloromycetin therapy (forty-fourth day of illness) temperature became normal. Chloromycetin was reduced to 250 mg. every four hours on the sixth day of

* Received for publication July 21, 1949.

treatment, and on the tenth day to every six hours. Treatment this time continued for 16 days. The temperature remained normal for the rest of the patient's hospital stay.

Urine cultures were all negative. Stool cultures became positive on the seventeenth day of illness (during chloromycetin therapy), and again became positive during the relapse, and were positive on the fifty-fifth day of illness after 16 days of chloromycetin (figure 1).

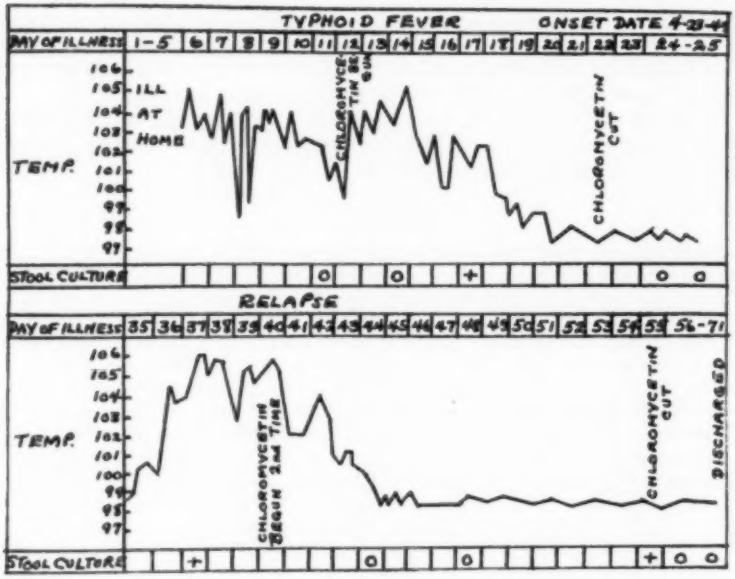
TYPHOID FEVER
ONSET DATE 4-29-4
DAY OF ILLNESS
1-5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24-25
TEMP.
ILL AT HOME
CHLOROMYCETIN CUT
STOOL CULTURE
RELAPSE
DAY OF ILLNESS
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56-71
TEMP.
CHLOROMYCETIN BEGUN 2nd TIME
CHLOROMYCETIN CUT
DISCHARGED
STOOL CULTURE

FIG. 1.

He was discharged after 66 days of hospitalization, to be observed by the New York Board of Health.

DISCUSSION

It was very apparent that chloromycetin favorably influenced the course of typhoid fever in this case. The patient's general condition improved within 48 hours after the start of treatment with lessened toxicity and diminishing fever. The blood stream promptly became sterilized, and the patient became alert and hungry. In spite of the continuation of the drug for seven days after the fever had come down to normal, a severe relapse occurred on the seventeenth day of normal temperature. The initial dose in the first treatment course was too small according to the dosage suggested by Woodward, due to a mistake in computing it. When the relapse occurred the dosage instituted was 250 mg. every hour until 50 mg./kg. had been reached, and then continued as described in the case report for a total of 16 days. The response to treatment during the relapse was better than when treated originally, which would indicate that in spite of

previous treatment and in spite of too small a dose during the first course of treatment no drug fastness had developed by the typhoid bacilli.

It was also apparent that while chloromycetin did sterilize the blood stream it did not sterilize the gastrointestinal tract, proved by the occurrence of, first, a severe relapse, and second, by failure to prevent the carrier state. Woodward et al. reported on the development of two serious complications among their 10 treated cases,—one of perforation and one of hemorrhage.

During the height of the fever when the patient was delirious and incontinent the oral administration of chloromycetin became extremely difficult. The rectal route was not attempted because of incontinence. It is to be hoped that an antibiotic may be developed which can be given parenterally as well as orally.

Summary

A case of typhoid fever treated with chloromycetin is presented. From this case and from reports in the literature it appears that both chloromycetin and to a lesser extent aureomycin favorably influence the course of the disease and are able to sterilize the blood stream, but that neither antibiotic, in the doses given, can be counted on to eradicate the bacilli from the gastrointestinal tract, or to prevent complications and relapses.

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EDITORIAL

NEW LIGHT ON THE MECHANISM OF THE AURICULAR ARRHYTHMIAS

SINCE the theory that circus movement was the mechanism underlying auricular flutter and fibrillation was first advanced and set on an apparently sound experimental basis by Lewis nearly 30 years ago, his teaching has been widely accepted and incorporated in most textbooks of physiology, pharmacology, medicine and cardiology. Only an occasional, and for the most part unheeded, voice has been raised in disagreement. But Prinzmetal and his colleagues, at the Institute for Medical Research in Los Angeles, have recently advocated an alternate concept of the genesis of these arrhythmias and backed it with what appears to be incontrovertible proof. In fact, if the camera does not lie, Lewis' circus appears to be folding its impregnable tents.

In perhaps the most original and fruitful cardiovascular research of the last few years, Prinzmetal and his coworkers [1] now claim to have proved that circus movement is not the underlying mechanism of auricular fibrillation and flutter; and that the auricular arrhythmias—ectopic beats, paroxysmal tachycardia, flutter and fibrillation—are all manifestations of one and the same abnormal mechanism, a single discharging ectopic focus. This they call "the unitary nature of the auricular arrhythmias."

Before considering their claims in detail, it is worth while to review briefly Lewis' evidence.[2] The idea of circus movement was originally suggested in 1908 by the demonstration of a circulating wave of contraction through a ring of tissue cut from the umbrella of the jelly fish.[3] A few years later rings of tissue cut from the auricles of fishes were shown to possess a similar capacity for sustaining circus movement [4]; and the same capacity was demonstrated in rings cut from the ventricles of turtles.[5]

With this suggestive background Lewis appeared to prove that a similar circus movement was the underlying mechanism of auricular flutter and fibrillation. He believed that a narrow elliptical band of muscle encircling the venae cavae was occupied by the main circulating wave, from which "daughter" waves were distributed to the remainder of the auricular muscle; and that in flutter the circus wave was regular, while that of fibrillation was erratic and pursued a shorter elliptical orbit. His experimental method was to induce flutter by electrical stimulation in the dog's auricle, and then to

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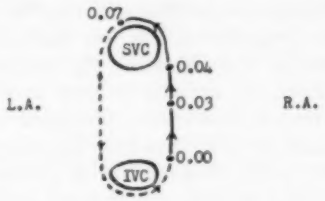
make two simultaneous electrocardiographic tracings—one a standard Lead II, and the other a direct lead from the auricular muscle. Times were measured at which the impulse reached various points in the auricular musculature, by measuring the intervals between an auricular summit in Lead II, and the corresponding intrinsic deflection of the direct lead. The results he obtained are most readily followed by reference to a much simplified and modified diagram:



Starting with the point 0.00 as zero, he found that the impulse arrived at consecutive points on the ellipse circumnavigating the venae cavae at approximately 0.03, 0.04 and 0.07 second respectively. He concluded that the impulse continued on its elliptical path until it again reached the neighborhood of the inferior vena cava, finally returning to the zero point and thence continuing as the next circulating impulse. The loophole in Lewis' experiments was the lack of direct measurements from the body of the left auricle. The arc of the circus path which occupied the body of this chamber was merely inferred. Lewis himself was well aware of the significance of this gap and referred to it as a "weakness" in his theory. But he substantiated his claims with what he thought was irrefutable electrocardiographic evidence. By timing the momentary atrial electrical axes of the flutter undulations in electrocardiographic leads, taken from points in the plane of the hypothetical circus wave, he concluded that the axes rotated through 360° during each auricular cycle. Prinzmetal and his colleagues have clearly shown, however, that this argument is based on imperfect understanding of the component parts of the flutter wave.[6] Thus Lewis' claims were insecurely founded on (a) a circus path, half of the circumference of which was only inferred to exist; and (b) an inevitably incomplete knowledge of the flutter wave on the electrocardiogram.

Needless to say, with the comparatively crude tools at his disposal, Lewis did superb pioneer work on the auricular arrhythmias, for which we all have the greatest respect and admiration; and none more than Dr. Prinzmetal, who formerly worked with him in London. With the technical refinements of two progressive decades, however, much has been brought to light which could not before be demonstrated. Thus Prinzmetal and his group have disproved Lewis' conclusions in two ways: first, by enlisting the candid eye of the movie camera; and secondly by a modification and extension of Lewis' own technic, for which they have recruited the multiple-channel electrocardio-

[6] Personal communication.

gram and the dual-beam, cathode-ray oscillograph. With this formidable battery of reinforcements, they have won a decisive victory over traditional theory.

By taking high-speed color cinematographs of the auricles of the intact dog's heart at speeds up to 2,000 frames a second, and then projecting them at eight frames a second, the movements of the auricles were slowed 250 times. In this "slow motion," events which occur in an actual time of one second, take four minutes to unfold themselves on the screen. To complete their ingenious technic a magnifying lens was used, so that a magnification of 100 times on projection was effected. By means of such pictures the auricular contraction wave can actually be seen in all its detail. All who witnessed the demonstration movie film presented by these investigators at Atlantic City last summer must have been impressed with the excellently clear and artistic results which this method of photography and projection can achieve. By the time of their preliminary report [1] the authors had studied over 75,000 feet of film on experimentally induced arrhythmias in more than 200 dogs.

In order to study the sequence of auricular events in fibrillation, this arrhythmia was induced by applying aconitine to the auricular muscle, as originally described by Matthews [7] in 1897, and more recently modified by Scherf,[8] or by electrical stimulation. When fibrillation was established, motion pictures disclosed that there were two distinct types of auricular contractions: minute, irregular, incessant contractions occurring at tremendous speeds—direct lead tracings showed a rate of 800 to 1600 per minute, while the more sensitive oscillograph revealed the incredible rate of up to 40,000 a minute. These contractions, and their corresponding electrocardiographic and oscillographic deflections, were labelled "M". These tiny "M" contractions were seen only in fibrillation, and these observers claim that they have indirect evidence which suggests that it is these which are largely responsible for the irregular ventricular response characteristic of this arrhythmia.

The second type of contractions were large, fairly regular and wavelike, and constituted the "fibrillation" which is visible to the unaided eye. These contractions occurred at a rate of 400 to 600 per minute and, although fairly regular in time, were not uniform in strength. They almost certainly correspond with the familiar "f" waves of the electrocardiogram. By careful observation of the auricles in slow motion, both individually and together, the authors could conclude that these waves did not pursue a circus path, and did not beget "daughter" waves as Lewis had postulated.

When in turn auricular flutter was induced and inspected by similar technic, it was seen to be characterized by contractions similar to the "L" contractions of fibrillation. These were, however, slower, more regular

[7] Matthews, S. A.: A study of the action of aconitine on the mammalian heart and circulation, J. Exper. Med. **2**: 593, 1897.

[8] Scherf, D.: Studies on auricular tachycardia caused by aconitine administration, Proc. Soc. Exper. Biol. and Med. **64**: 233, 1947.

and more vigorous, but again no evidence of a circus path was seen. The wave of contraction did not involve a narrow band of muscle, but occupied the entire width of the auricle. The auricular appendices contracted almost simultaneously, whereas, if a circus movement controlled the arrhythmia, one appendix should be seen on the film to contract at least several seconds before the other. Furthermore, when flutter was produced by applying aconitine at a central point in the right auricular wall, the contraction wave could be seen to originate at that point and to spread away from it in all directions equally and simultaneously; thus, although typical flutter had been generated, there was no evidence of its waves pursuing a unidirectional path.

Another experimental method which supported the evidence against circus movement was the following: strategically cutting, or burning, the auricular muscle in the path of the hypothetical circus (which should interrupt the continuous circulation of the movement if it existed) was without effect on the persistence of fibrillation or flutter.

When paroxysmal tachycardia was induced, the auricular contractions appeared similar to those which were seen in flutter. Their rate of occurrence, however, was slower, and consequently each auricular contraction was followed by a ventricular response. In other words, tachycardia was simply a comparatively slow flutter with a 1:1 conduction ratio. Observation of films also confirmed that the auricular wave of an isolated ectopic beat was exactly similar to the individual waves of paroxysmal tachycardia. Thus all the arrhythmias were characterized by contraction waves visually indistinguishable from the "L" waves of fibrillation.

Two further experiments confirmed the suspected unitary nature of the arrhythmias. First, auricular fibrillation was induced by a drop of 0.2 per cent aconitine on the auricular muscle. The investigators then cooled (by spraying with ethyl chloride, or by applying ice) the ectopic focus from which the fibrillary waves were originating and found that, as the temperature fell and the rate of discharge slowed, the rhythm of the heart usually passed consecutively through flutter and tachycardia, and finally reached the stage of sinus rhythm interspersed with ectopic beats originating from the cooled aconitine focus. Conversely, as the focus was then allowed to thaw, the arrhythmias usually recurred in reverse order. They found, moreover, as Scherf had also demonstrated, that by manipulating the amount of aconitine applied and the temperature of the focus, any desired arrhythmia could be maintained. The deciding factor appeared to be simply the rate of discharge of impulses from the ectopic focus. Thus, for example, a "critical" level, varying from 300 to 600 per minute in different animals, determined that flutter should pass into fibrillation.

Again, a similar sequence of events could be produced by electrical stimulation. By this technic the rate of effective stimuli could, of course, be accurately controlled at will. Thus as the rate was increased from 100 to

600, it was often possible to produce the same sequence of ectopic beats, tachycardia, flutter and fibrillation, in that order.

Not content with the revelations of the movie camera, Prinzmetal and his coworkers extended and modified Lewis' own experimental method. By the method in general use in his time, the body of the left auricle could not be sufficiently exposed to permit proper electrocardiographic studies to be made with paired electrodes. There was, therefore, the considerable hiatus in Lewis' circus pathway to which reference has already been made. Prinzmetal and his associates have, on the other hand, obtained wide exposure of the left auricle and thus have been able to use exploring electrodes in both auricles. These experiments were carried out in 30 dogs, and consistent results were obtained.

When flutter was produced by an aconitine focus close to the inferior vena cava, and electrodes were placed equidistant (2 cm.) from the focus, one in each auricle, the impulse was found to arrive at each point almost simultaneously, instead of arriving at one point some time before the other as would be expected if the impulse were following a circus path. Again, if two electrodes were placed in the body of the right auricle, one at 1 cm. and one at 4 cm. from the focus, it was found, as expected, that the impulse reached the nearer electrode before it reached the more remote. Exactly the same finding was obtained, however, when two comparably situated electrodes were applied in the body of the left auricle. In other words, in both auricles the impulse was traveling *away from* the aconitine focus. If a circus pathway existed this would not have been so, for the impulse in one auricle would have been on its "return journey" *towards* the focus.

The evidence that flutter is not a manifestation of circus movement was further and significantly confirmed in human patients. By means of esophageal leads, taken at serial levels, they were able to show conclusively that in most cases of human flutter the wave travelled from the caudal end of the auricle cephalad, and there was no return wave as there would be if circus movement prevailed.[8] In this connection it is interesting to note that in the course of their experiments with dogs they had found the most effective site for the production of flutter by means of aconitine to be at the *caudal* end of the auricle close to the inferior vena cava.

Thus, by at least five different methods—from visual observation of experimentally induced flutter in dogs, to electrocardiographic analysis in man—these authors have brought redoubtable evidence against the existence of circus movement in the fluttering auricle.

It should not be overlooked that Scherf, independently but by a similar aconitine method, has also come to the conclusion that auricular fibrillation and flutter are initiated by rapid impulse formation in a single center, and not by circus movement.[9]

One of the lessons to be learned from this work is that old theories are never so good that they need not be tested with new methods. When a

[9] Scherf, D., Romano, F. J., and Terranova, R.: Experimental studies on auricular flutter and auricular fibrillation. Am. Heart J. 36: 241, 1948.

scientist has earned a great and formidable reputation, there is a tendency to vest all his utterances with almost oracular authority. Lesser lights are inclined to feel, *"Oraculum dixit,* if that is what the master thought, who are we to differ?" We should, however, rather whet our critical faculties and prepare to challenge any theory, no matter how generally accepted, unless it be backed by immaculate and total proof.

An interesting and stimulating effect of this work will be the reëxamination of many of the classically accepted mechanisms of action of quinidine and digitalis in the auricular arrhythmias. Many a categorical statement by many a high authority, based on the supposition of circus movement, must be scrutinized and reëvaluated. If this recent work is substantiated, we can no longer agree that quinidine stops auricular fibrillation when, as Osler phrased it, "the head of the circulating wave catches up with its tail." Likewise, we cannot subscribe to the statement that "quinidine slows the speed of the circus movement in the auricle" as has been recently reiterated.[10] We cannot agree that digitalis tends to fix fibrillation because it increases the rate of the circus movement. We must inquire why it is that digitalis converts flutter to fibrillation; it cannot be that it increases the speed and irregularity of the circuit.

The revelations of Prinzmetal, together with the blow that McMichael [11] has recently struck at the traditional action of digitalis, should stimulate much further research into the mechanism of action of the cardiac glycosides. It may not be out of place here to make a plea—that those who attempt to elucidate further the actions of these glycosides should clearly state the specific substance with which they are experimenting, and should apply their results to that glycoside alone. There should, for example, be no experiments with strophanthin and then loose transference of results to "digitalis"—a too common practice in the past to which attention has already been drawn.[12] A decided qualitative difference between the actions of g-strophanthin (ouabain) and digoxin has been demonstrated [11]; it is therefore clearly unscientific to obtain results with one glycoside and apply them uncritically to the generic "digitalis."

Apart from the main trends of the work here reviewed, many other interesting related issues have engaged the attention of Prinzmetal and his colleagues during the past three years of their investigation. Among other things they have made interesting observations on the pumping capacity of the auricles, on the action of digitalis on the fibrillating auricle, and on the action of strophanthin on the auricles in experimentally induced congestive failure. To learn the full details of these and other studies to which they have devoted their attention, we must wait impatiently for the publication of their book, "The Auricular Arrhythmias," scheduled to appear in about a year.

H. J. L. M.

[10] Gold, H.: Quinidine in disorders of the heart, 1950, Paul B. Hoeber, Inc. N. Y.
[11] McMichael, J.: The pharmacology of the failing heart, Brit. Med. J. 2: 927, 1948.
[12] Leading Article, Brit. Med. J. 2: 947, 1948.

REVIEWS

Diseases of the Heart. By CHARLES K. FRIEDBERG, M.D., Associate Physician, Mt. Sinai Hospital, New York; Lecturer in Medicine, Columbia University. 1081 pages; 17 × 25 cm. W. B. Saunders Company, Philadelphia. 1949. Price, $11.50.

This new volume on diseases of the heart deserves a place among the classic texts on cardiology. It is an exceedingly good, well written, and complete book. The material is clearly presented, with basic physiology and pathogenesis lucidly described; but not to the detriment of the clinical aspects of cardiac disease, which are also pictured in deserved detail. The bibliography is unusually complete and includes many papers published as late as 1949. The index facilitates ready reference to the text.

The common types of cardiac disease are dealt with in detail. Many of the less common cardiac disorders are also described, and the rarer affections of the heart are more briefly considered. In all instances the bibliography is amazingly complete. The sections on congenital heart disease and the heart in hyperthyroidism are very nicely presented. The discussion of insurance and medico-legal problems in cardiology is well done. There is no introductory section on physical examination of the heart, nor of the findings in a normal heart. While these are included as part of the discussion of different diseases, it might be well to include such a section in the next edition.

In reviewing such a comprehensive text, it is difficult to single out any particular section for comment. Where the subject is a controversial one, the author presents the pertinent arguments for both sides, and while not dogmatic, properly presents his own opinion.

Because of the current interest in certain cardiac problems, the author's views on certain subjects are worthy of quotation. After evaluating the arguments for and against the use of digitalis in acute myocardial infarction, he states: "In the absence of more convincing objections, it has been my practice to administer digitalis for the treatment of heart failure even in the first few days after myocardial infarction unless the heart failure is readily controlled by the more immediate measures of bed rest, opiates, oxygen therapy, and occasionally venesection." He believes that, "There is no significant basis to justify (the) routine use (of quinidine) for the purpose of preventing these arrhythmias." In the treatment of arteriosclerotic heart disease, "Theoretically it would be desirable to direct treatment against the basic cause, namely arteriosclerosis . . . there is no convincing evidence that any of these measures actually prevent, delay, or reverse the arteriosclerotic process in humans."

Speaking of Fiedler's myocarditis, "It is doubtful whether the cases included in this category form an etiologic, pathologic or clinical entity." He does not recommend sympathectomy in relatively early cases of hypertension, believing that, "Sympathectomy should be reserved for patients with severe and progressive manifestations who do not respond to medical therapy." He is noncommittal regarding the rice diet and describes good results with salt restriction in hypertensives. "The results of sulfonamide prophylaxis to prevent rheumatic recurrences have not been sufficiently impressive, considering the risks and practical difficulties involved, to justify the universal application of this measure." As for radioactive iodine, "It seems highly probable that this promising form of treatment will replace both thyroidectomy and antithyroid drugs in the treatment of thyrocardiacs."

This book is a detailed, well-integrated text, interestingly presented, and attractively printed. It should prove invaluable to both novices and experts in cardiology.

S. S.

Quinidine in Disorders of the Heart. By HARRY GOLD, M.D., Professor of Clinical Pharmacology at Cornell University Medical College. 115 pages; 13 × 21.5 cm. Paul B. Hoeber, Inc., New York. 1950. Price, $2.00.

This little book is exactly what would be anticipated from its title and the name of its author. It is a treatise dealing with all aspects of quinidine therapy and bears the expected stamp of high authority and wide experience in both pharmacological and clinical fields. In the author's words it is "a personal account . . . based on experience with successes and failures, readings, and reflection in relation to this subject during a period of about twenty-five years." This work has been prompted by his belief that only a fraction of the usefulness of quinidine is effectively exploited in practice.

Dr. Gold emphasizes that this is mainly the result of rigid dosage systems not based on an adequate understanding of the drug's action. Each patient should be handled individually with a clear appreciation of both the aim to be achieved and the potentialities of quinidine. With this in mind the author has written a lucid book with particular stress on the mechanism of quinidine actions, therapeutic and toxic, the why and wherefore of dosage systems and the rationale of recommended precautions.

The first chapters deal with general topics such as indications, actions, effects on electrocardiogram, blood levels, dosage, and so forth; then each arrhythmia is considered in turn; and finally special aspects of quinidine therapy are covered, including its use in coronary thrombosis and in anesthesia and surgery, and a valuable section on the controversial subject of the combined use of quinidine and digitalis. In conclusion a bibliography of 137 references gives a valuable cross section of the literature of the subject since 1906.

There is little that can be said of this monograph except in praise. It achieves its purpose admirably and should be of inestimable value to general practitioners—for whom it is primarily intended—as well as to students, internists and cardiologists.

H. J. L. M.

Acute Appendicitis and Its Complications. By FREDERICK FITZHERBERT BOYCE, M.D., Assistant Professor of Clinical Surgery, Tulane University School of Medicine. 487 pages; 15.5 × 23.5 cm. Oxford University Press, New York. 1949. Price, $8.75.

This is a most timely and complete monograph on the commonest of surgical diseases. It is particularly timely because of all of the recent work reported concerning the use of the ever growing list of antibiotics in the treatment of appendicitis and peritonitis. The author does not discredit the judicious use of these agents in lowering the mortality of the complications of acute appendicitis. However, with mature surgical advice, he strongly emphasizes that these agents in no way substitute for early surgery.

The book includes ample review of the more recent literature with an abundance of statistics on all phases of the disease. The difficulties of correct diagnoses are well illustrated with case reports, which include many bizarre clinical pictures. Complications of acute appendicitis and their treatment are ably and concisely presented.

Altogether, this monograph is probably the best work on the subject presently available.

H. C. H.

Allergy in Relation to Otolaryngology. 1st Ed. By FRENCH K. HANSEL, M.D., M.S., F.A.C.A., Editor-in-Chief, Annals of Allergy; Director of The Hansel Foundation; Associate Professor of Otolaryngology, Washington University School of Medicine. 77 pages; 14 × 20 cm. Bruce Publishing Company. 2642 University Avenue, St. Paul 4, Minnesota. 1949. Price, $2.50.

This book consists of a general discussion of allergy in relation to otolaryngology by the primary author, Dr. Hansel. His discussion of the part played by allergy in nasal conditions would seem to be adequate, and he is to be commended for his conservatism concerning the value of surgery in nasal conditions. Those of us who are familiar with Dr. Hansel's writings know that he places great stress and great reliance upon the cytologic picture in nasal smears. It is his opinion that the numbers and types of cells present are of major diagnostic significance, particularly in differentiating between allergic manifestations and infections.

Dr. Hansel covers this subject rather exhaustively and gives an elaborate method of interpretation that, in his opinion, is of great diagnostic value. The reviewer believes that possibly the author overemphasizes its value.

The panel discussion, following the major presentation and participated in by nine men, rather fully covers different phases of the field including the use of radium, surgery, and the psychosomatic approach. This section will serve as a useful summary of the present status of our knowledge in this field.

Unfortunately nothing new is added to diminish our deficit of precise knowledge as to effective therapy of these conditions. It seems that until some new door of knowledge is opened, our contribution to the satisfactory handling of these clinical entities will be considerably less than ideal.

H. M. B.

Manual of Medical Emergencies. By STUART C. CULLEN, M.D., and E. G. GROSS, M.D. 267 pages; 12.5 × 18 cm. Year Book Publishers, Inc., Chicago. 1949. Price, $3.75.

The book reviewer should always bear in mind that he owes more to the prospective reader than to the author—he reviews for the reader's guidance and not the author's gratification. This attitude is perhaps more than ever applicable in reviewing a manual for emergency and therefore vital use; such a book should obviously be of the highest quality.

This small volume which is pocket-sized, is clearly and readably printed. The illustrations are helpful and in places amusing. The first two chapters are excellent and deal with Airway, Artificial Respiration and Oxygen Therapy. There follows a more mediocre chapter on Circulatory Emergencies and then an adequate summary of the therapy of Acute Poisonings. The fifth and sixth chapters are good and deal with Local Anesthetic Drug Reactions and Head Injuries respectively. There follows an account of Allergic Disturbances which leaves much to be desired, and one wonders in passing what possible stretch of classification justifies the inclusion of hay fever as an emergency.

The eighth section deals with the control of severely agitated and convulsive patients, while the next covers the care of the comatose patient, acute and chronic. "Protracted coma" is not in itself an emergency, and one feels that some of the 12 pages devoted to this subject would have been better spent in elaborating more fully on the differential diagnosis of comas of recent onset—one of the commonest and most baffling of emergency situations. The tenth chapter on miscellaneous emergencies covers gastric dilatation, burns, sunstroke and heat exhaustion. In additional sections, the authors discuss technics of venipuncture, and give a list of useful emergency drugs with their preparations and sources. In this list, however, it is

amazing and amusing to find that nearly one fifth of the space occupied by the total list is devoted to tabulating no less than a dozen of those comparatively untried, and certainly in any emergency rather readily dispensed with preparations, the antihistamines. The authors obviously have a soft spot in their hearts for these drugs, for in the text they apply this rather flattering unction to them, "The antihistamines have not been entirely successful in asthma." As a gentle dismissal of their virtual uselessness in the severe asthmatic attack, this is hard to beat.

In a manual of emergency treatment, designed to be readily available for perusal in the emergency, clearly a most desirable attribute are simple, lucid, clearcut instructions which leave no doubt in the reader's mind of his proper course of action. For the most part this clarity is achieved; but occasionally the reader is left in the air at a time when, obviously, it is most salutary that he should have both feet firmly on the ground. Thus in dealing with ventricular fibrillation we are told that it may be interrupted by "the use of electric shock, as described by Beck." This is dangerously inadequate and calls for amplification. Similarly, before attempting to transport the patient in it, one would like to have something more descriptive than "modified Schaefer posture." Again the "solution of starch" recommended for use for gastric lavage in iodine poisoning, deserves more detailed description. The statements that isuprel "usually causes a fall in blood pressure" and "causes no blood pressure effects" are not only contradictory but also misleading: many instances of a pressor effect have been reported.

The authors adopt the sensible expedient of giving all dosages in both metric and apothecary equivalents; in at least four instances, however, the equivalents are inaccurate; for example, the dosage of intravenous quinidine is given as "0.2 — 0.4 mg. (3½ — 6½ grs.)."

If this book is reviewed with more emphasis on its defects than on its virtues, it is only because it is a book of great potential value. It has tremendous possibilities all of which have not been realized. The fact that perhaps the most sought after lecture by senior students is one on "Medical Emergencies," testifies to the potential popularity and importance of a book of this kind; and its perfection should be proportionate to these qualities. Although this is a good book, it could and should be even better.

H. J. L. M.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Angina Pectoris and Myocardial Infarction, With Special Reference to the Autonomic Nervous System. By HEYMAN R. MILLER, M.D., Formerly Principal Physician and Chief, Signal Corps Climatic Research, etc. 336 pages; 23.5 × 15.5 cm. 1950. Grune & Stratton, Inc., New York. Price, $8.75.

Antibiotics: A Survey of Penicillin, Streptomycin, and Other Antimicrobial Substances from Fungi, Actinomycetes, Bacteria, and Plants. Volume I and Volume II. By H. W. FLOREY, M.A., M.D., Ph.D., F.R.S.; E. CHAIN, M.A., Ph.D., F.R.S.; N. G. HEATLEY, M.A., Ph.D.; M. A. JENNINGS, M.A., B.M.; A. G. SANDERS, M.A., M.B., D.Phil.; E. P. ABRAHAM, M.A., D.Phil., and M. E. FLOREY, M.B., B.S. 1774 pages (total, both volumes); 25.5 × 16 cm. 1950. Oxford University Press, New York. Price, $29.75 (volumes not sold separately).

Brain and Behaviour: Induction as a Fundamental Mechanism of Neuro-psychic Activity: An Experimental and Clinical Study with Consideration of Educational, Mental-hygienic and General Sociological Implications. By N. E. ISCHLONDSKY,

M.D. 184 pages; 25.5 × 15.5 cm. 1949. The C. V. Mosby Company, Saint Louis. Price, $7.00.

Brucellosis (Undulant Fever), Clinical and Subclinical. 2nd ed. By HAROLD J. HARRIS, J.D., F.A.C.P., with the assistance of BLANCHE L. STEVENSON, R.N.; Foreword by WALTER M. SIMPSON, M.S., M.D., F.A.C.P. 617 pages; 24 × 16 cm. 1950. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

An Introduction to the Study of Experimental Medicine. By CLAUDE BERNARD. Translated by HENRY COPLEY GREENE, A.M.; with an Introduction by LAWRENCE J. HENDERSON, Professor of Biological Chemistry, Harvard University. 226 pages; 23.5 × 15.5 cm. 1949. Henry Schuman, Inc., New York. Price, $3.00.

L'Angiopatia Acuta Trombotica Necrosante dei Reni: Contributo Allo Studio Della Necrosi Corticale Bilaterale dei Reni—Omnia Medica, Supplemento XXII. By LUIGI MIGONE. 164 pages; 24.5 × 17 cm. (paper-bound). 1949. Instituto di Ricerche v. Baldacci Editore, Pisa.

Lehrbuch der Inneren Medizin. By M. BROGLIE, Schleswig; H. DENNIG, Stuttgart; K. HANSEN and W. GRONEMEYER, Lübeck; N. HENNING, Würzburg; A. HEYMER, Essen; H. REINWEIN, Kiel; F. SCHELLONG, Münster; G. SCHALTENBRAND, Würzburg, and H. SCHULTEN, Köln. 999 pages, 24.5 × 17.5 cm. 1950. Georg Thieme Verlag, Stuttgart. Price: Ganzleinen DM 29.70.

Louis Pasteur, Free Lance of Science. By RENE J. DUBOS. 418 pages; 22.5 × 15 cm. 1950. Little, Brown & Company, Boston. Price, $5.00.

Malnutrition and Starvation in Western Netherlands, September, 1944 to July, 1945. Part I (Appendices, Part II). 187 pages, Part I; 299 pages, Part II; 24 × 17 cm. (paper-bound). 1948. General State Printing Office, The Hague.

Mitchell-Nelson's Textbook of Pediatrics. 5th ed. Edited by WALDO E. NELSON, M.D., Professor of Pediatrics, Temple University School of Medicine, etc., with the Collaboration of Sixty-three Contributors. 1658 pages; 26.5 × 18 cm. 1950. W. B. Saunders Company, Philadelphia. Price, $12.50.

The Physiological Basis of Medical Practice: A Text in Applied Physiology. 5th ed. By CHARLES HERBERT BEST, C.B.E., M.A., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada), Professor and Head of Department of Physiology, Director of the Banting-Best Department of Medical Research, University of Toronto; and NORMAN BURKE TAYLOR, V.D., M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lon.), Professor of the History of Medicine and Medical Literature, University of Western Ontario, London, Canada, etc. 1330 pages; 26 × 18 cm. The Williams & Wilkins Company, Baltimore. Price, $11.00.

Practical Neurological Diagnosis, With Special Reference to the Problems of Neurosurgery. 4th ed. By R. GLEN SPURLING, M.D., Clinical Professor of Surgery (Neurosurgery), University of Louisville School of Medicine. 268 pages; 23.5 × 15.5 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $5.00.

Proceedings of the First National Cancer Conference. 310 pages; 23.5 × 15 cm. 1949. American Cancer Society and The National Cancer Institute of the U. S. Public Health Service, Federal Security Agency, New York.

Quinidine in Disorders of the Heart. By HARRY GOLD, M.D., Professor of Clinical Pharmacology at Cornell University Medical College, etc. 115 pages; 21 × 13 cm. 1950. Paul P. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $2.00.

Report of the Medical Research Council for the Years 1945–1948. Presented by the Lord President of the Council to Parliament by Command of His Majesty, October, 1949. 183 pages; 24.5 × 15 cm. (paper-bound). 1949. His Majesty's Stationery Office, London. Price, 5 shillings net.

The Sexual Perversions and Abnormalities: A Study in the Psychology of Paraphilia. 2nd ed. By CLIFFORD ALLEN, M.D., M.R.C.P., D.P.M., Physician in Charge of the Psychiatric Department of the Seamen's Hospital, Greenwich, etc. 346 pages; 22.5 × 14 cm. 1950. Oxford University Press, New York. Price, $5.00.

A Short History of Physiology. 2nd ed. By KENNETH J. FRANKLIN, D.M., F.R.C.P., Professor of Physiology at the Medical College of St. Bartholomew's Hospital. 147 pages; 22 × 14 cm. 1950. Staples Press, Inc., New York. Price, $2.00.

A Story of Nutritional Research: The Effect of Some Dietary Factors on Bones and the Nervous System. (The Abraham Flexner Lectures Series Number Nine). By SIR EDWARD MELLANBY, G.B.E., M.D., Sc.D., F.R.S., Secretary of the British Medical Research Council, etc. 454 pages; 21 × 13.5 cm. 1950. Published for Vanderbilt University by The Williams & Wilkins Company, Baltimore. Price, $5.00.

COLLEGE NEWS NOTES

Regional Meetings

The Annual Regional Meeting of the American College of Physicians for Maryland, the District of Columbia, and Delaware was held in Baltimore on February 25, 1950, under the Governorship of Dr. Wetherbee Fort, F.A.C.P. The program for this meeting was given in detail in the March issue of the Annals. This proved to be a most successful meeting, both from the point of view of subject material and from the attendance. The total attendance was 366.

The Annual Regional Meeting of the College for Colorado, Idaho, New Mexico, Montana and Wyoming was held at Denver, February 21, 1950, with an attendance of 126. The meeting was directed under the Governorship of Dr. Ward Darley, F.A.C.P., of Colorado, with the coöperation of Dr. S. M. Poindexter, F.A.C.P., Governor for Idaho, Dr. Walter I. Werner, F.A.C.P., Governor for New Mexico, and Dr. Harold W. Gregg, F.A.C.P., Governor for Montana and Wyoming. Dr. Louis S. Faust, F.A.C.P., Denver, was chairman of the program committee. Dr. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect of the College, gave a paper on "The Collagen Diseases" and was the chief speaker at the banquet in the evening. It was considered the most successful regional meeting yet conducted in the region.

The 1950 Annual Regional Meeting of the College for Oklahoma and Arkansas will be held in Tulsa, September 30, 1950, at the Mayo Hotel, under the Governorships of Dr. Wann Langston, F.A.C.P., of Oklahoma, and Dr. Arless A. Blair, F.A.C.P., of Arkansas.

The 1950 Annual Regional Meeting of the College for Western New York is scheduled to be held on October 14, 1950, in Rochester, under the Governorship of Dr. Edward C. Reifenstein, Sr., F.A.C.P.

The Annual Northwest Regional Meeting of the College will be held in Portland, Oregon, November 10–11, 1950, under the Chairmanship of Dr. Howard P. Lewis, F.A.C.P., Governor for Oregon. This meeting will be for the states of Oregon, Washington, Montana, Wyoming, and Idaho, and the provinces of British Columbia and Alberta, Canada. Invitations will also be sent to members in Manitoba and Saskatchewan.

The Annual Regional Meeting of the College for Kentucky is scheduled to be held in Lexington on December 9, 1950, under the Governorship of Dr. J. Murray Kinsman, F.A.C.P.

The Annual Mid-West Regional Meeting of the College will be held in Madison, Wisconsin, on November 18, 1950, under the Chairmanship of Dr. Karver L. Puestow, F.A.C.P., Governor for Wisconsin. This meeting will be for the states of Illinois, Indiana, Iowa, Michigan, Minnesota, and Wisconsin.

The 1950 Annual Regional Meeting of the College for North Carolina will be held during the autumn in Chapel Hill, North Carolina, under the Governorship of Dr. Paul F. Whitaker, F.A.C.P.

The Annual Regional Meeting of the College for New Jersey will be held November 1, 1950, in Trenton, under the Governorship of Dr. George H. Lathrope, F.A.C.P.

Research Fellowships—The American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1951—June 30, 1952. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They

are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1950. Announcement of awards will be made November, 1950.

A. C. P. Postgraduate Courses

The following courses on the Spring, 1950, schedule have been concluded:

Course No. 2, DISEASES OF THE BLOOD VESSELS, Cornell University Medical College and the New York Hospital, New York, N. Y.; Irving S. Wright, M.D., F.A.C.P., Director. This proved to be a most popular course on its initial appearance on our program, with a registration of 100.

Course No. 3, RECENT DEVELOPMENTS IN THE CARDIOVASCULAR FIELD, Michael Reese Hospital Postgraduate School, Chicago, Ill.; Louis N. Katz, M.D., F.A.C.P., Director. At the time this news note is prepared, March 14, the registration is 66.

Courses yet to be given include the following:

Course No. 4, ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION, Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., Director. May 8–13, 1950. Fees: A.C.P. Members, $50.00; Non-Members, $120.00. This course has been registered to capacity for several weeks.

Course No. 5, ENDOCRINOLOGY, University of Illinois College of Medicine, Chicago, Ill.; Willard O. Thompson, M.D., F.A.C.P., Director. May 15–20, 1950. Fees: A.C.P. Members, $30.00; Non-members, $50.00.

Officers of Instruction

Dwight E. Clark, M.D., Associate Professor of Surgery, University of Chicago School of Medicine.

Warren H. Cole, M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Illinois College of Medicine; Surgeon-in-Chief, Research and Educational Hospitals.

Arthur R. Colwell, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School.

Albert Dorfman, M.D., Assistant Professor of Pediatrics, University of Chicago School of Medicine; Director of Research, La Rabida Sanitarium.

Ray F. Farquharson, M.D., F.A.C.P., Professor and Head of the Department of Medicine, University of Toronto Faculty of Medicine; Physician-in-Chief, Toronto General Hospital.

Smith Freeman, M.D., Professor and Chairman of the Department of Experimental Medicine, Northwestern University Medical School.

E. C. Hamblen, M.D., F.A.C.S., Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Chief, Division of Endocrinology and Endocrinologist, Duke Hospital; Durham, N. C.

Norris J. Heckel, M.D., F.A.C.S., Clinical Professor of Urology, Department of Surgery, University of Illinois College of Medicine.

Edward Henderson, M.D., Director of Clinical Research, Schering Corporation.

DWIGHT J. INGLE, Ph.D., Senior Research Scientist (Physiology), The Upjohn Research Laboratories.

ANDREW C. IVY, Ph.D., M.D., D.Sc., LL.D., F.A.C.P., Distinguished Professor of Physiology and Head of the Department of Clinical Science, University of Illinois College of Medicine; Vice President, University of Illinois in charge of the Chicago Professional Colleges.

ROBERT W. KEETON, M.D., F.A.C.P., Professor and Head of the Department of Medicine, University of Illinois College of Medicine.

ALLAN T. KENYON, M.D., Professor of Medicine, University of Chicago School of Medicine.

DAVID E. MARKSON, M.D., F.A.C.P., Associate Professor of Medicine, Northwestern University Medical School.

E. PERRY MCCULLAGH, M.D., F.A.C.P., Head, Section of Endocrinology and Metabolism, Cleveland Clinic, Cleveland, Ohio.

IRVINE MCQUARRIE, M.D., Professor and Head of the Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minn.

JOHN R. MOTE, M.D., Medical Director, Pharmaceutical Medical Control, The Armour Laboratories.

WARREN O. NELSON, M.D., Professor of Anatomy, State University of Iowa College of Medicine, Iowa City, Iowa.

THERON G. RANDOLPH, M.D., Instructor in Medicine, Northwestern University Medical School.

EDWARD F. ROSENBERG, M.D., F.A.C.P., Assistant Professor of Medicine, Chicago Medical School; Chief, Arthritis Clinic, Michael Reese Hospital.

EDWARD H. RYNEARSON, M.D., F.A.C.P., Associate Professor of Medicine, University of Minnesota Graduate School of Medicine (Mayo Foundation); Consultant, Division of Medicine, Mayo Clinic, Rochester, Minn.

DANELY P. SLAUGHTER, M.D., Assistant Professor of Surgery, University of Illinois College of Medicine; Director, Outpatient Tumor Clinic, Research and Educational Hospitals.

SAMUEL SOSKIN, M.D., F.A.C.P., Professorial Lecturer in Physiology, University of Chicago School of Medicine; Director, Medical Research Institute, Michael Reese Hospital; Dean, Michael Reese Hospital Postgraduate School.

WILLARD O. THOMPSON, M.D., F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine.

HENRY H. TURNER, M.D., F.A.C.P., Clinical Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

WALTMAN WALTERS, M.D., F.A.C.S., Professor of Surgery, University of Minnesota Graduate School of Medicine (Mayo Foundation); Head of a Division of Surgery, Mayo Clinic; Rochester, Minn.

Presiding Officers

LOWELL T. COGGESHALL, M.D., F.A.C.P., Frederick H. Rawson Professor of Medicine and Dean, Division of Biological Sciences, University of Chicago School of Medicine.

WARREN H. COLE, M.D., F.A.C.S. (see Officers of Instruction).

GEORGE H. COLEMAN, M.D., F.A.C.P., Associate Professor Emeritus of Medicine, Northwestern University Medical School.

THOMAS J. COOGAN, M.D., F.A.C.P., Associate in Medicine, Northwestern University Medical School.

LESTER R. DRAGSTEDT, M.D., F.A.C.P., F.A.C.S., Professor of Surgery and Chairman of the Department, University of Chicago School of Medicine.

EDMUND F. FOLEY, M.D., F.A.C.P., Professor of Medicine, University of Illinois College of Medicine.

WARREN W. FUREY, M.D., Assistant Clinical Professor of Roentgenology, Stritch School of Medicine of Loyola University.

N. C. GILBERT, M.D., F.A.C.P., Emeritus Professor and Chairman of the Department of Medicine, Northwestern University Medical School.

HARRY M. HEDGE, M.D., F.A.C.P., Assistant Professor of Dermatology, Northwestern University Medical School.

FORD K. HICK, M.D., F.A.C.P., Associate Professor of Medicine, University of Illinois College of Medicine.

ERNEST E. IRONS, M.D., F.A.C.P., Clinical Professor of Medicine Emeritus, University of Illinois College of Medicine.

MALCOLM T. MACEACHERN, M.D., F.A.C.P., Associate Professor Emeritus of Medicine, Northwestern University Medical School; Director, Program in Hospital Administration, The School of Commerce, Northwestern University.

IRVINE MCQUARRIE, M.D. (see Officers of Instruction).

WALTER L. PALMER, M.D., F.A.C.P., Professor of Medicine, University of Chicago School of Medicine.

PAUL S. RHOADS, M.D., F.A.C.P., Professor of Medicine, Northwestern University Medical School; Chief of Medicine, Wesley Memorial Hospital.

EDWARD H. RYNEARSON, M.D., F.A.C.P. (see Officers of Instruction).

KENNETH SCATLIFF, M.D., Secretary, Chicago Medical Society.

JOHN J. SHEININ, M.D., Dean and Chairman of the Department of Anatomy, Chicago Medical School.

LEROY H. SLOAN, M.D., F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine.

F. LEE STONE, M.D., Clinical Assistant Professor of Obstetrics and Gynecology Emeritus, University of Illinois College of Medicine.

WILLARD O. THOMPSON, M.D., F.A.C.P. (see Officers of Instruction).

THEODORE R. VANDELLEN, M.D., F.A.C.P., Associate Professor of Medicine and Assistant Dean, Northwestern University Medical School.

ALBERT VANDERKLOOT, M.D., Clinical Associate Professor of Medicine, University of Illinois College of Medicine.

GEORGE E. WAKERLIN, M.D., F.A.C.P., Professor and Head of the Department of Physiology, University of Illinois College of Medicine.

WALTMAN WALTERS, M.D., F.A.C.S. (see Officers of Instruction).

RICHARD H. YOUNG, M.D., F.A.C.P., Dean and Professor of Medicine, Northwestern University Medical School.

A considerable amount of time will be devoted to the clinical uses of ACTH and Cortisone and related steroids.

This course will provide an intensive review of recent developments in the field of endocrinology, including endocrine gynecology and sterility. Special attention will be paid to clinical disorders, and physiological and biochemical developments will be presented in relation to their bearing on the interpretation of clinical phenomena.

Leading teachers from all over the United States and Canada will take part in the course. Endocrine disorders will be illustrated by presentation of patients. There will be a round-table discussion each day at luncheon in which all men on the faculty that day will participate. This will provide an opportunity for the men taking the course to discuss various problems informally with the teachers. There will be morning and afternoon sessions each day except on Saturday, when there will be a morning session only.

Meeting Place: Illinois Room, La Salle Hotel, Chicago. The physical facilities for the course are excellent. The management has assured us that they will make every

effort to serve us well. It has been our experience that it is more convenient for the men taking a postgraduate course of this type to have it in a hotel rather than in the medical school. Everything is under one roof, and no time is lost in transportation.

Hotel Accommodations: Full arrangements have been concluded for the housing of the registrants, as well as the housing of the course itself, at the La Salle Hotel, La Salle St. at Madison Ave., Chicago, Mr. M. P. Mathewson, Sales Director. The hotel announces that those who plan to attend the course would have a better choice of accommodations if they would plan to arrive on Sunday, May 14. Rates: Single rooms, $5.00–$8.00; double rooms, $7.00–$10.00; twin-bedded rooms, $9.50–$12.00; two rooms connecting bath for 4, $13.50–$15.00; suites, $9.50–$25.00. When writing for accommodations address request to Mr. Mathewson and identify yourself with this course and with the College.

Intermissions: There will be a short intermission every morning and afternoon during which light refreshments will be served at a nominal charge.

Outline of Course

Monday, May 15. Illinois Room, La Salle Hotel.

A.M. Session.

Dr. Willard O. Thompson, Presiding

8:00– 9:00 Registration. La Salle Hotel, Mezzanine Floor near Illinois Room.

9:00– 9:30 Radio-Active Iodine in the Treatment of Graves' Disease and Toxic Nodular Goiter.
Dr. McCullagh.

9:30–10:00 The Use of Radio-Active Iodine in the Treatment of Hyperthyroidism and Carcinoma of the Thyroid.
Dr. Clark.

10:00–10:30 Hypothyroidism in Children.
Dr. Turner.

10:30–10:45 Intermission.

Dr. Richard H. Young, Presiding

10:45–11:15 The Present Status of Propyl Thiouracil in the Treatment of Hyperthyroidism.
Dr. McCullagh.

11:15–11:45 Treatment of Hyperthyroidism.
Dr. Cole.

11:45–12:15 Endocrine Regulation of Growth.
Dr. Thompson.

12:15–12:45 Effects of Endocrine Agents on Connective Tissue.
Dr. Dorfman.

12:45– 2:00 Luncheon—Century Room, 19th Floor.

P.M. Session.

Dr. Lowell T. Coggeshall, Presiding

2:00– 2:30 Clinical Syndromes of Adrenal Cortical Hyperactivity.
Dr. Turner.

2:30– 3:00 The Present Status of ACTH.
Dr. Mote.

3:00– 3:30 Metabolic Effects of ACTH on Human Subjects.
Dr. Freeman.

3:30– 3:45 Intermission.

Dr. Malcolm T. MacEachern, Presiding

3:45– 4:15 The Effects of ACTH on a Patient with Sheehan's Syndrome.
Dr. Freeman.

4:15– 4:45 Testicular Failure.
Dr. McCullagh.

4:45– 5:45 Presentation of Patients.
Discussion by Drs. Clark, Cole, Dorfman, Freeman, McCullagh, Mote, Thompson and Turner.

Tuesday, May 16. Illinois Room, La Salle Hotel.
A.M. Session.

Dr. Ford K. Hick, Presiding

9:00– 9:30 Pathogenesis of Spontaneous Hypoglycemosis and the Place of Adrenocorticotropic Hormone (ACTH) in Its Treatment.
Dr. McQuarrie.

9:30–10:00 Trials with Pregneninolone.
Dr. Henderson.

10:00–10:30 Tumors of the Pancreas, Including Hyperfunctioning Tumors of the Islands of Langerhans.
Dr. Walters.

10:30–10:45 Intermission.

Dr. Kenneth Scatliff, Presiding

10:45–11:15 Tumors of the Pancreas, Including Hyperfunctioning Tumors of the Islands of Langerhans (continued).
Dr. Walters.

11:15–11:45 Pituitary-Testicular Dysfunctions in Male Hypogonadism.
Dr. Turner.

11:45–12:15 The Etiology and Treatment of Macrogenitosomia Precox in Children.
Dr. McQuarrie.

12:15–12:45 Hyaluronidase.
Dr. Dorfman.

12:45– 2:00 Luncheon—Century Room, 19th Floor.
Dr. Waltman Walters, Presiding

P.M. Session.

Dr. Warren W. Furey, Presiding

2:00– 2:30 Diagnosis and Treatment of Addison's Disease.
Dr. McCullagh.

2:30– 3:00 Endocrine Problems of Childhood.
Dr. Turner.

3:00– 3:30 Cushing's Syndrome: Metabolic and Clinical Studies.
Dr. McQuarrie.

3:30– 3:45 Intermission.

Dr. George E. Wakerlin, Presiding

3:45– 4:15 Tumors of the Suprarenal Gland with Special Reference to Hyperfunctioning Tumors.
Dr. Walters.

4:15– 4:45 Tumors of the Suprarenal Gland with Special Reference to Hyperfunctioning Tumors (continued).
Dr. Walters.

4:45– 5:45 Presentation of Patients.
Discussion by Drs. Dorfman, Henderson, McCullagh, McQuarrie, Turner and Walters.

Wednesday, May 17. Illinois Room, La Salle Hotel.
A.M. Session.

Dr. Theodore R. VanDellen, Presiding

9:00– 9:30 Endocrinology and Treatment of Functional Uterine Hemorrhage.
Dr. Hamblen.

9:30–10:00 The Role of the Adrenal Cortex in Organic Metabolism.
Dr. Ingle.

10:00–10:30 Postpubescent Amenorrhea.
Dr. Hamblen.
10:30–10:45 Intermission.
Dr. George H. Coleman, Presiding
10:45–11:15 The Female Climacteric.
Dr. Hamblen.
11:15–11:45 Diseases of the Adrenal Glands in Children.
Dr. McQuarrie.
11:45–12:15 Rheumatoid Arthritis—Experiences with Hormone Therapy.
Dr. Rosenberg.
12:15–12:45 Use of ACTH and Cortisone in Various Allergic States.
Dr. Randolph.
12:45– 2:00 Luncheon—Grand Ballroom.
Dr. Irvine McQuarrie, Presiding.

P.M. Session.

Dr. Thomas J. Coogan, Presiding
2:00– 2:30 Uses and Misuses of Sex Hormones.
Dr. Thompson.
2:30– 3:00 Interpretation of the Testicular Biopsy.
Dr. Nelson.
3:00– 3:30 The Valuation of Sex Hormones in the Treatment of Male Sterility.
Dr. Heckel.
3:30– 3:45 Intermission.
Dr. Edmund F. Foley, Presiding
3:45– 4:15 Functional Interrelations between Hypophysis, Gonads and Adrenal Cortex.
Dr. Nelson.
4:15– 4:45 Management of Arthritis with ACTH.
Dr. Markson.
4:15– 5:45 Presentation of Patients.
Discussion by Drs. Hamblen, Heckel, Ingle, Markson, McQuarrie, Nelson, Randolph, Rosenberg and Thompson.

Thursday, May 18. Illinois Room, La Salle Hotel.

A.M. Session.

Dr. Harry M. Hedge, Presiding
9:00– 9:30 Physiopathology of the Testis.
Dr. Nelson.
9:30–10:00 Male Pseudohermaphroditism.
Dr. Hamblen.
10:00–10:30 Androgen and Estrogen Production in the Human Testis.
Dr. Nelson.
10:30–10:45 Intermission.
Dr. Ernest E. Irons, Presiding
10:45–11:15 The Diagnosis and Treatment of Male Infertility.
Dr. Heckel.
11:15–11:45 The Relationship of the Adrenal Cortex to Nitrogen Balance and Growth.
Dr. Ingle.
11:45–12:15 Anterior Pituitary Insufficiency (Simmonds' Disease and Milder Syndromes).
Dr. Farquharson.
12:15–12:45 The Effect of Prolonged Ingestion of Thyroid (at various dosage levels) in Patients with an Intact Thyroid Gland.
Dr. Farquharson.

12:45– 2:00 Luncheon—Grand Ballroom.
Dr. Willard O. Thompson, Presiding.

P.M. Session.
Dr. John J. Sheinin, Presiding

2:00– 2:30 Testicular Tumors.
Dr. Nelson.

2:30– 3:00 Endocrinology Therapy in the Treatment of Diseases of the Prostate Gland.
Dr. Heckel.

3:00– 3:30 Types of Hypogonadism and Their Treatment.
Dr. Thompson.

3:30– 3:45 Intermission.
Dr. Walter L. Palmer, Presiding

3:45– 4:15 Effects of Steroids upon the Testis.
Dr. Nelson.

4:15– 4:45 Anorexia Nervosa.
Dr. Farquharson.

4:45– 5:45 Presentation of Patients.
Discussion by Drs. Farquharson, Hamblen, Heckel, Ingle, Nelson and Thompson.

Friday, May 19. Illinois Room, La Salle Hotel.

A.M. Session.
Dr. N. C. Gilbert, Presiding

9:00– 9:30 The Properties of Pituitary Agents in Man.
Dr. Kenyon.

9:30–10:00 Pituitary Insufficiency vs. Anorexia Nervosa.
Dr. Rynearson.

10:00–10:30 Hypopituitarism.
Dr. Kenyon.

10:30–10:45 Intermission.
Dr. Paul S. Rhoads, Presiding

10:45–11:15 Is Obesity an Endocrine Problem?
Dr. Rynearson.

11:15–11:45 Gout: Diagnostic and Therapeutic Considerations.
Dr. Rosenberg.

11:45–12:15 Cushing's Syndrome vs. Adrenogenital Syndrome.
Dr. Rynearson.

12:15–12:45 Functions of the Adrenal Cortex.
Dr. Thompson.

12:45– 2:00 Luncheon—Century Room, 19th Floor.
Dr. Edward H. Rynearson, Presiding

P.M. Session.
Dr. F. Lee Stone, Presiding

2:00– 2:30 The Gastrointestinal Hormones.
Dr. Ivy.

2:30– 3:00 The Gastrointestinal Hormones (continued).
Dr. Ivy.

3:00– 3:30 Parathyroid Insufficiency.
Dr. Rynearson.

3:30– 3:45 Intermission.
Dr. Albert Vanderkloot, Presiding

3:45– 4:15 Hyperparathyroidism.
Dr. Rynearson.

4:15– 4:45 ACTH in the Treatment of Rheumatic Fever.
Dr. Dorfman.
4:45– 5:45 Presentation of Patients.
Discussion by Drs. Dorfman, Ivy, Kenyon, Rosenberg, Rynearson and Thompson.

Saturday, May 20. Illinois Room, La Salle Hotel.
A.M. Session.
Dr. LeRoy H. Sloan, Presiding
9:00– 9:30 The Etiology of Diabetes.
Dr. Keeton.
9:30–10:00 Problems in the Treatment of Diabetes Mellitus.
Dr. Colwell.
10:00–10:30 Hyperinsulinism vs. Functional Hypoglycemia.
Dr. Rynearson.
10:30–10:45 Intermission.
Dr. Lester R. Dragstedt, F.A.C.P., Presiding
10:45–11:15 The Metabolic Disturbance in Diabetes Mellitus.
Dr. Soskin.
11:15–11:45 Diabetes and the Cardiovascular System.
Dr. Soskin.
11:45–12:15 Rheumatoid Arthritis—Experiences with Hormone Therapy.
Dr. Rosenberg.
12:15–12:45 Rôle of Hormones in the Treatment of Cancer.
Dr. Slaughter.

Course No. 6, THE DYNAMICS OF METABOLIC DISEASES, New York University Post-Graduate Medical School, New York, N. Y.; Clarence E. de la Chapelle, M.D., F.A.C.P., Director; Charles F. Wilkinson, Jr., M.D., Associate Director. May 15–20, 1950. **Fees: A.C.P. Members, $30.00; Non-members, $60.00.**

Officers of Instruction

Benjamin I. Ashe, M.D., F.A.C.P., Associate Clinical Professor of Medicine, New York University Post-Graduate Medical School.
David P. Barr, M.D., F.A.C.P., Professor of Medicine, Cornell University Medical College; Physician-in-Chief, New York Hospital.
Robert Boggs, M.D., Dean, New York University Post-Graduate Medical School.
Maurice Bruger, M.D., F.A.C.P., Associate Professor of Medicine, New York University Post-Graduate Medical School.
Joseph J. Bunim, M.D., Associate Professor of Medicine, New York University College of Medicine.
Clarence E. de la Chapelle, M.D., F.A.C.P., Professor of Medicine and Associate Dean, New York University Post-Graduate Medical School; Director of Medicine, Lenox Hill Hospital.
A. Wilbur Duryee, M.D., F.A.C.P., Professor of Clinical Medicine, New York University Post-Graduate Medical School.
Richard H. Freyberg, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Cornell University Medical College; Director of Arthritis Clinic, New York Hospital; Director of Department of Internal Medicine, Hospital for Special Surgery.
Herbert Gershberg, M.D., Fellow in Medicine, New York University College of Medicine.

IRVING GRAEF, M.D., Assistant Professor of Clinical Medicine, New York University College of Medicine.

EDWARD F. HARTUNG, M.D., Associate Clinical Professor of Medicine, New York University Post-Graduate Medical School.

J. WILLIAM HINTON, M.D., F.A.C.S., Professor of Surgery and Chairman of the Department, New York University Post-Graduate Medical School; Director of Surgery, University Hospital and Bellevue Hospital (Fourth Surgical Division).

WALTER KUHL, M.D., Fellow in Medicine, New York University College of Medicine.

ROBERT F. LOEB, M.D., F.A.C.P., Bard Professor of Medicine, Columbia University College of Physicians and Surgeons; Director, Medical Service, Presbyterian Hospital.

JERE W. LORD, JR., M.D., F.A.C.S., Assistant Professor of Surgery, New York University Post-Graduate Medical School.

COLIN M. MACLEOD, M.D., Professor of Microbiology and Chairman of the Department, New York University College of Medicine.

CURRIER MCEWEN, M.D., F.A.C.P., Associate Professor of Medicine and Dean, New York University College of Medicine.

SEVERO OCHOA, M.D., Professor of Pharmacology and Chairman of the Department, New York University College of Medicine.

KARL R. PALEY, M.D., Clinical Assistant in Medicine, New York University College of Medicine.

HERBERT POLLACK, M.D., F.A.C.P., Lecturer in Medicine, Columbia University College of Physicians and Surgeons; Chief of Metabolism Section, Mount Sinai Hospital.

JOSEPH POST, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, New York University College of Medicine.

ELAINE P. RALLI, M.D., F.A.C.P., Associate Professor of Medicine, New York University College of Medicine.

RULON W. RAWSON, M.D., Associate Professor of Medicine, Cornell University Medical College; Chief, Division of Clinical Investigation, Sloan Kettering Institute; Chief, General Medicine, Memorial Hospital.

L. CORSAN REID, M.D., Associate Professor of Physiology, New York University College of Medicine.

LEON SOKOLOFF, M.D., Instructor in Pathology, New York University College of Medicine.

CHARLES F. WILKINSON, JR., M.D., Professor of Medicine and Chairman of the Department, New York University Post-Graduate Medical School; Director of Medicine, University Hospital and Bellevue Hospital (Fourth Medical Division).

Methods and Purpose of the Course: The course is designed to offer experience, both basic and clinical, in recent developments in the field of internal medicine with emphasis on the diagnosis and treatment of altered metabolic states. The clinical application of the more recent physiological and biochemical advances will be presented by means of seminars. Didactic presentations will be kept to a minimum. The program will be mainly informal, evolved by means of conferences, clinics, seminars and panels with adequate opportunity for participation by members of the course.

The libraries of the New York Academy of Medicine, the New York University-Bellevue Medical Center as well as that of Bellevue Hospital will be available to registrants of the course.

Parking facilities on the Medical Center grounds will be available to all registrants.

This, a new course on the College schedule, should be a most excellent one. Facilities are still available for additional registrants.

Outline of Course

Monday, May 15.
A.M. Session.

New York University Post-Graduate Medical School

477 First Avenue

New York, N. Y.

9:00– 9:30 Registration.
9:30–10:00 Welcome—Dean Boggs.
Main Lecture Hall.

SYMPOSIUM ON ALTERED CARBOHYDRATE METABOLISM

Bellevue Hospital

A2 B2 Conference Room

10:10–11:00 Fundamentals of Carbohydrate Metabolism.
Dr. Ochoa.
11:05–11:50 Diabetes Mellitus.
Dr. Ashe.
12:00–12:45 Vascular Complications of Diabetes Mellitus.
Dr. Duryee.

P.M. Session.

University Hospital

Erdmann Auditorium

2:00– 3:00 The Diabetic Patient as a Surgical Risk.
Dr. Lord.
3:00– 3:15 Intermission.
3:15– 4:00 Functional Hypoglycemia.
Dr. Wilkinson.
4:00– 5:00 Organic Hypoglycemia.
Dr. Wilkinson.

Tuesday, May 16.
A.M. Session.

University Hospital

Erdmann Auditorium

9:00–10:45 Panel on the Management of Deranged Carbohydrate Metabolism.
Drs. Ashe, Ochoa, Ralli and Wilkinson.
10:45–11:00 Intermission.

SYMPOSIUM ON DISEASES OF THE LIVER

11:00–12:00 Liver Physiology as a Basis for Liver Function Tests.
Dr. Wilkinson.
12:05–12:50 Pathological Aspects of Liver Disease.
Drs. Post and Sokoloff.

P.M. Session.

Bellevue Hospital

A2 B2 Conference Room

2:00– 3:00 Cirrhosis of the Liver.
Dr. Ralli.

3:00– 3:15 Intermission.
3:15– 5:00 Panel on Miscellaneous Affections of the Liver.
Drs. Graef, MacLeod, Post, Ralli and Wilkinson.

Wednesday, May 17.
A.M. Session.

Bellevue Hospital

C & D Amphitheater

9:00–10:00 Clinical Pathological Conference.

SYMPOSIUM ON METABOLIC JOINT DISEASES

Bellevue Hospital

A2 B2 Conference Room

10:00–10:50 Pathogenesis and Classification of Arthritis.
Dr. Hartung.
11:00–12:45 The Rôle of the Pituitary and Adrenals in Rheumatic Diseases.
Dr. Bunim.
P.M. Session.

University Hospital

Erdmann Auditorium

2:00– 3:00 Purine Metabolism.
Dr. Bruger.
3:00– 3:15 Intermission.
3:15– 5:00 Seminar on Gout and Arthritis (with demonstration of patients).
Drs. Bruger, Bunim, Freyberg (by invitation), Hartung and McEwen.

Thursday, May 18.
A.M. Session.

University Hospital

Erdmann Auditorium

9:00– 9:55 Fundamentals of Lipid Metabolism.
Dr. Bruger.
10:00–10:45 Newer Concepts in the Genesis of Atherosclerosis.
Dr. Wilkinson.
10:45–11:00 Intermission.
11:00–11:50 Obesity.
Dr. Ralli.
12:00–12:45 Malnutrition Precipitated by Disease.
Dr. Pollack (by invitation).
P.M. Session.

Bellevue Hospital

A2 B2 Conference Room

2:00– 4:30 including intermission. Clinic on Adrenal and Pituitary Diseases.
Presentation of Patients: Drs. Ralli, Gershberg and Kuhl.
Discussion: Dr. Loeb (by invitation).

Friday, May 19.
A.M. Session.

SYMPOSIUM ON THYROID DYSFUNCTION

Bellevue Hospital

A2 B2 Conference Room

9:00– 9:50 Physiology of the Thyroid.
Dr. Bruger.
10:00–10:45 Cardiovascular Aspects of Altered Thyroid Function.
Dr. de la Chapelle.
10:45–11:00 Intermission.
11:00–11:45 The Rôle of the Isotopes in the Study of Thyroid Disease.
Dr. Rawson (by invitation).
12:00–12:45 Surgical Aspects of Thyroid Disease.
Dr. Hinton.

P.M. Session.

Bellevue Hospital

A2 B2 Conference Room

2:00– 2:45 Diseases of the Parathyroid.
Dr. Barr (by invitation).
2:45– 3:00 Intermission.
3:00– 5:00 Panel on the Management of Thyroid Diseases (with presentation of cases, medical and surgical).
Drs. Barr (by invitation), Bruger, Hinton, de la Chapelle, Paley, Ralli, and Rawson (by invitation).

Saturday, May 20.
A.M. Session.

SYMPOSIUM ON MINERAL METABOLISM

Bellevue Hospital

A2 B2 Conference Room

9:00– 9:45 Iron Metabolism.
Dr. Reid.
9:45–10:00 Intermission.
10:00–10:45 Calcium Metabolism.
Dr. Reid.
10:45–12:00 Clinic: Hemochromatosis.
Dr. Graef.

Course No. 7, TRENDS AND NEWER DEVELOPMENTS IN INTERNAL MEDICINE, Temple University School of Medicine, Philadelphia, Pa.; Thomas M. Durant, M.D., F.A.C.P., Director. June 5–10, 1950. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Officers of Instruction

J. EDWARD BERK, M.D., F.A.C.P., Assistant Professor of Medicine, Temple University School of Medicine.

GEORGE I. BLUMSTEIN, M.D., Associate in Medicine, Temple University School of Medicine.

WILBUR E. BURNETT, M.D., F.A.C.S., Professor of Surgery and Head of the Department, Temple University School of Medicine.

W. Edward Chamberlain, M.D., F.A.C.P., Professor of Radiology and Head of the Department, Temple University School of Medicine.

R. Philip Custer, M.D., Assistant Professor of Pathology, University of Pennsylvania School of Medicine; Director of Laboratories, Presbyterian Hospital.

Garfield G. Duncan, M.D., F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College of Philadelphia: Director of Medical Division and of the Benjamin Franklin Clinic, Pennsylvania Hospital.

Thomas M. Durant, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine; Visiting Physician, Philadelphia General Hospital.

W. Wallace Dyer, M.D., F.A.C.P., Associate Professor of Medicine, University of Pennsylvania School of Medicine; Chief, Diabetic Section, Hospital of the University of Pennsylvania.

William E. Ehrich, M.D., Professor of Pathology, University of Pennsylvania Graduate School of Medicine; Chief, Division of Pathology, Philadelphia General Hospital.

O. Spurgeon English, M.D., F.A.C.P., Professor of Psychiatry and Head of the Department, Temple University School of Medicine.

George E. Farrar, Jr., M.D., F.A.C.P., Associate Professor of Medicine, Temple University School of Medicine.

Donald R. Fitch, M.D., Instructor in Medicine, Hahnemann Medical College and Hospital of Philadelphia.

Harrison F. Flippin, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine; Visiting Physician, Philadelphia General Hospital.

Francis M. Forster, M.D., Associate Professor of Neurology, Jefferson Medical College of Philadelphia.

Herbert Freed, M.D., Assistant Professor of Psychiatry, Temple University School of Medicine; Visiting Psychiatrist and Chief, Child Psychiatry Clinic, Philadelphia General Hospital.

Sherman F. Gilpin, Jr., M.D., Clinical Professor of Neurology, Temple University School of Medicine.

Joseph L. Hollander, M.D., F.A.C.P., Assistant Professor of Internal Medicine, University of Pennsylvania Graduate School of Medicine; Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine; Chief, Arthritis Section, Hospital of the University of Pennsylvania.

Harold L. Israel, M.D., F.A.C.P., Assistant Professor of Medicine, Woman's Medical College of Pennsylvania; Visiting Physician, Eagleville Sanatorium.

Thomas A. Johnson, M.D., F.A.C.P., Associate Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine.

Luke W. Jordan, M.D., Instructor in Orthopedics, Temple University School of Medicine.

Richard A. Kern, M.D., F.A.C.P., Professor of Medicine and Head of the Department, Temple University School of Medicine; Chief of Medical Service, Temple University Hospital.

John Lansbury, M.D., F.A.C.P., Associate Professor of Medicine, Temple University School of Medicine.

Joan Humphrey Long, M.D., Instructor in Research Surgery, Temple University School of Medicine.

Stanley H. Lorber, M.D., Instructor in Medicine and Research Associate, Samuel S. Fels Research Institute, Temple University School of Medicine.

Francis R. Manlove, M.D., Assistant Professor of Medicine, Temple University School of Medicine.

EDWARD S. MCCABE, M.D., Instructor in Medicine, Temple University School of Medicine; Assistant Visiting Physician, Philadelphia General Hospital.

EDWIN B. MCLEAN, M.D., Instructor in Pediatrics, Temple University School of Medicine; Hematologist, Abington Memorial and St. Christopher's Hospitals.

M. J. OPPENHEIMER, M. D., Professor of Physiology and Head of the Department, Temple University School of Medicine.

WILLIAM H. PERLOFF, M.D., Instructor in Medicine, University of Pennsylvania School of Medicine; Chief, Endocrine Clinic, Philadelphia General Hospital.

EDWARD C. REIFENSTEIN, JR., M.D., F.A.C.P., Executive Director, Medical and Research Division, Ayerst, McKenna and Harrison, Ltd.; Research Associate, Sloan-Kettering Institute, Memorial Cancer Center, New York, N. Y.

ROBERT ROBBINS, M.D., Instructor in Radiology, Temple University School of Medicine; Director of Radiotherapy, Temple University Hospital.

GEORGE P. ROSEMOND, M.D., F.A.C.S., Clinical Professor of Surgery, Temple University School of Medicine.

HARRY SHAY, M.D., F.A.C.P., Clinical Professor of Medicine and Director, Samuel S. Fels Research Institute, Temple University School of Medicine.

LOUIS A. SOLOFF, M.D., F.A.C.P., Assistant Professor of Medicine, Temple University School of Medicine.

HERBERT M. STAUFFER, M.D., Associate Professor of Radiology, Temple University School of Medicine.

CHARLES M. THOMPSON, M.D., F.A.C.P., Professor and Head of Department of Gastro-enterology, Hahnemann Medical College and Hospital of Philadelphia; Visiting Physician, Philadelphia General Hospital.

LEANDRO M. TOCANTINS, M.D., Associate Professor of Medicine, Jefferson Medical College of Philadelphia; Hematologist, Pennsylvania Hospital.

HAROLD S. TUFT, M.D., Assistant Instructor in Medicine (Im.), Temple University School of Medicine; Chief, Allergy Clinic, Montgomery Hospital (Norristown); Assistant Pathologist, Mt. Sinai Hospital.

LOUIS TUFT, M.D., Assistant Professor of Medicine, Temple University School of Medicine; Chief, Allergy Clinic, Temple University Hospital.

STEWART WOLF, M.D., Associate Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, New York Hospital, New York, N. Y.

This course will present in concise fashion many of the trends and newer developments in the rapidly advancing field of Internal Medicine. An entire day will be devoted to Endocrinology and Metabolism and another full day to Diseases of the Gastro-intestinal Tract. Half days will be allotted to Cardiovascular Diseases, Pulmonary Diseases and Antibiotics, Allergy, Hematology, Arthritis, and Neurology and Psychiatry. Case presentations will accompany many of the discussions. Sufficient time will be provided for question and answer periods. Special emphasis will be placed upon those developments in the various fields which have practical therapeutic application. The "Pituitary-Adrenal Axis" and many of its recently discovered relationships will be included in both the Endocrinology and Arthritis Symposia. Panel discussions will feature several of the symposia. The subjects have been selected with great care, and the faculty includes members of the teaching staffs of near-by medical schools, in addition to those on the faculty of Temple University School of Medicine.

Place of Meeting: Much of the didactic part of the course will be given in the Auditorium of the American College of Physicians, 4200 Pine St. This will be concentrated into certain days. The clinical work will be given in the Erny Amphitheater of Temple University Hospital Annex, 3401 North Broad St.

Outline of Course

Note: A 10 to 15 minute interval has been left between papers for question and answer period.

Monday, June 5.

Auditorium

American College of Physicians

4200 Pine Street

A.M. Session. CARDIOVASCULAR DISEASES.
8:30 Registration.
9:00– 9:30 Pathophysiology of Congestive Failure.
Dr. Oppenheimer.
9:45–10:15 Some Aspects of Chronic Circulatory Failure Apparently Refractory to Mercurial Diuretics.
Dr. Soloff.
10:30–10:45 Intermission.
10:45–11:15 Atherosclerosis; Genesis and Management.
Dr. Durant.
11:30–12:00 Peripheral Vascular Disease. Newer Therapeutic Measures.
Dr. Manlove.
P.M. Session. PULMONARY DISEASE.
2:00– 2:30 Practical Pulmonary Function Tests.
Dr. Long.
2:45– 3:15 Pulmonary Insufficiency.
Dr. Durant.
3:30– 3:45 Intermission.

ANTIBIOTICS, ETC.

3:45– 4:15 Streptomycin and Para-Aminosalicylic Acid in the Treatment of Tuberculosis.
Dr. Israel.
4:30– 5:15 Aureomycin, Chloramphenicol and Terramycin.
Dr. Flippin.

Tuesday, June 6.

Erny Amphitheater, Temple University Hospital

3401 North Broad Street

A.M. Session. ALLERGY.
9:00– 9:30 Methods of Diagnosis in Allergic Diseases.
Dr. Louis Tuft.
9:45–10:15 Status Asthmaticus.
Dr. Blumstein.
10:15–10:30 Intermission.
10:30–11:00 Value and Limitations of Antihistaminic Drugs.
Dr. Kern.
11:15–11:45 Newer Sympathomimetic Drugs and Other Antibronchospasmodics.
Dr. Harold Tuft.
P.M. Session. NEUROLOGY.
2:00– 2:30 Parkinsonism with Emphasis on Newer Therapy.
Dr. Gilpin.

2:45– 3:15 Epilepsy.
Dr. Forster.
3:30– 3:45 Intermission.
3:45– 4:15 Mental Depression, Including Shock Therapy and Its Indications.
Dr. Freed.
4:30– 5:15 The Common Denominator in the Functional Conditions of Everyday Practice.
Dr. English.

Wednesday, June 7.

Erny Amphitheater, Temple University Hospital

3401 North Broad Street

A.M. Session. HEMATOLOGY.
9:00– 9:45 Lymph Node Disease—Clinical and Pathological Differentiation.
Dr. Custer.
10:00–10:30 Therapy of the Leukemias and Lymphoblastomata.
Dr. McLean.
10:30–10:45 Intermission.
10:45–11:30 Physiological Basis of the Treatment of Hemorrhagic Disease.
Dr. Tocantins.
11:45–12:15 Therapy of the Megaloblastic Anemias.
Dr. Farrar.
P.M. Session. ARTHRITIS.
Dr. John Lansbury, Presiding
2:00– 3:30 Panel Discussion—Therapy of Rheumatoid Arthritis.
Drs. Lansbury, Hollander, Jordan and Fitch.
3:30– 3:45 Intermission.
3:45– 4:15 Gout.
Dr. McCabe.
4:30– 5:00 Roentgenologic Diagnosis of Joint Disease and Therapy of Spondylitis.
Dr. Stauffer.

Thursday, June 8.

Auditorium

American College of Physicians

4200 Pine Street

A.M. Session. ENDOCRINOLOGY AND METABOLISM.
9:00– 9:45 Adrenal Relationships and the Adaptation Syndrome.
Dr. Ehrich.
10:00–10:45 Laboratory Aids to Diagnosis of Adrenal Cortical Disease.
Dr. Perloff.
11:00–11:15 Intermission.
11:15–12:00 Postmenopausal Osteoporosis.
Dr. Reifenstein.
P.M. Session
2:00– 3:30 Symposium on Thyroid Disease.
Drs. Perloff, Burnett and Robbins.
3:30– 3:45 Intermission.
3:45– 4:15 Obesity.
Dr. Duncan.
4:30– 5:00 Experience with New Insulins and Insulin Mixtures.
Dr. Dyer.

Friday, June 9.

Erny Amphitheater, Temple University Hospital

3401 North Broad Street

A.M. Session. GASTROINTESTINAL DISEASES.
Dr. Harry Shay, Presiding

9:00– 9:20 Pathophysiology of Jaundice.
Dr. Shay.

9:30– 9:50 Liver Function Tests.
Dr. Shay.

10:00–10:20 Needle Biopsy of the Liver.
Dr. Berk.

10:30–10:45 Intermission.

10:45–11:25 Portal Cirrhosis.
(A) Medical Management.
Dr. Thompson.
(B) Surgical Management of Its Complications.
Dr. Rosemond.

11:35–11:55 Evaluation of External Pancreatic Secretion as an Aid in the Differential Diagnosis of Disease of the Pancreas and Biliary Tract.
Dr. Lorber.

12:05–12:25 Chronic Recurrent Pancreatitis.
Dr. Berk.

P.M. Session.
Dr. Thomas A. Johnson, Presiding

2:00– 2:20 Functional Colopathies.
Dr. Lorber.

2:30– 3:10 Psychosomatic Aspects of Organic Gastrointestinal Disease.
Dr. Wolf.

3:20– 3:30 Intermission.

3:30– 5:00 Panel Discussion—Peptic Ulcer.
Drs. Johnson, Wolf, Burnett, Berk, Lorber, Shay, and Chamberlain.

Course No. 8, INTERNAL MEDICINE, University of California Medical School, San Francisco, Calif. Stacy R. Mettier, M.D., F.A.C.P., Director, June 19–23, 1950. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Officers of Instruction

PAUL M. AGGELER, M.D., Assistant Clinical Professor of Medicine, University of California Medical School.

THEODORE L. ALTHAUSEN, M.D., F.A.C.P., Professor of Medicine, University of California Medical School.

LESLIE L. BENNETT, Ph.D., M.D., Associate Professor of Medicine and Physiology, University of California Medical School.

ELBRIDGE J. BEST, M.D., Assistant Clinical Professor of Medicine, University of California Medical School.

HOWARD R. BIERMAN, M.D., Associate Clinical Professor of Experimental Oncology, University of California Medical School.

WARREN L. BOSTICK, M.D., Assistant Professor of Pathology, University of California Medical School.

N. RENE BOTHEREAU, M.D., Clinical Instructor in Medicine, University of California Medical School.

Henry D. Brainerd, M.D., Assistant Clinical Professor of Medicine and Pediatrics, University of California Medical School; Assistant Clinical Professor of Pediatrics, Stanford University School of Medicine.

Ellen Brown, M.D., Assistant Professor of Medicine, University of California Medical School.

Leela S. Craig, M.D., Clinical Instructor in Medicine, University of California Medical School.

Morris E. Dailey, M.D., Instructor in Medicine, University of California Medical School.

R. Lowry Dobson, M.D., Instructor in Medical Physics, University of California Medical School.

Matthew J. Ellenhorn, M.D., Assistant in Medicine, University of California Medical School.

Ephraim P. Engleman, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of California Medical School.

Roberto F. Escamilla, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of California Medical School.

Ernest H. Falconer, M.D., F.A.C.P., Clinical Professor of Medicine, University of California Medical School.

Minnie B. Goldberg, M.D., Assistant Clinical Professor of Medicine, University of California Medical School.

Gilbert S. Gordan, Jr., Ph.D., M.D., Instructor in Medicine and Pharmacology, University of California Medical School.

John M. Graves, M.D., Associate Clinical Professor of Dermatology, University of California Medical School.

Harold E. Hand, M.D., Assistant Clinical Professor of Medicine, University of California Medical School.

H. Corwin Hinshaw, M.D., F.A.C.P., Clinical Professor of Medicine, Stanford University School of Medicine.

James J. Hopper, M.D., Assistant Professor of Medicine, University of California Medical School.

Ernest Jawetz, Ph.D., M.D., Associate Professor of Bacteriology and Lecturer in Medicine and Pediatrics, University of California Medical School.

William J. Kerr, M.D., F.A.C.P., Professor of Medicine and Chairman, Division of Medicine, University of California Medical School.

Laurance W. Kinsell, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of California Medical School.

John B. Lagen, M.D., Associate Professor of Medicine, University of California Medical School.

John H. Lawrence, M.D., Associate Professor of Experimental Medicine and Associate Professor of Medical Physics, University of California Medical School; Consultant in Internal Medicine, Student Health Service, and Director, Donner Laboratory, University of California, Berkeley.

Sanford E. Leeds, M.D., F.A.C.S., Clinical Instructor in Surgery, University of California Medical School.

Maurice E. Leonard, M.D., Assistant Clinical Professor of Medicine, University of California Medical School.

Howard P. Lewis, M.D., F.A.C.P., Professor of Medicine and Chairman of the Department, University of Oregon Medical School, Portland, Ore.

Hans Lisser, M.D., F.A.C.P., Clinical Professor of Medicine, University of California Medical School.

Salvatore P. Lucia, M.D., Sc.D., F.A.C.P., Professor of Medicine and Lecturer in Medical History and Bibliography, University of California Medical School.

JOHN A. LUETSCHER, JR., M.D., Associate Professor of Medicine, Stanford University School of Medicine.

CHARLES D. MARPLE, M.D., Lecturer in Medicine and Coordinator of Cardiovascular Board, University of California Medical School.

GORDON MEIKLEJOHN, M.D., C.M., Assistant Professor of Medicine, University of California Medical School.

STACY R. METTIER, M.D., F.A.C.P., Professor of Medicine and Head of Postgraduate Instruction (Medical Extension), University of California Medical School.

EARL R. MILLER, M.D., Professor of Radiology, University of California Medical School.

JACQUES NOWAK, M.D., Instructor in Pediatrics and Research Associate in Pediatrics and Medicine, University of California Medical School.

ERNEST W. PAGE, M.D., Associate Professor of Obstetrics and Gynecology, University of California Medical School.

WALTER L. PALMER, M.D., F.A.C.P., Professor of Medicine, University of Chicago School of Medicine, Chicago, Ill.

LOWELL A. RANTZ, M.D., Associate Professor of Medicine, Stanford University School of Medicine.

JAMES F. RINEHART, M.D., Professor of Pathology, University of California Medical School.

JOHN J. SAMPSON, M.D., Associate Clinical Professor of Medicine, University of California Medical School.

DONALD R. SMITH, M.D., Assistant Clinical Professor of Urology, University of California Medical School.

MAURICE SOKOLOW, M.D., F.A.C.P., Assistant Professor of Medicine, University of California Medical School.

DWIGHT L. WILBUR, M.D., F.A.C.P., Clinical Professor of Medicine, Stanford University School of Medicine.

The purpose of this course is to present a review of the newer methods of treatment and diagnosis of diseases pertaining to Internal Medicine. The use of new drugs in the treatment of cardiovascular and blood dyscrasia will be emphasized. There will also be a symposium on chemotherapy that will be outstanding in character and will be presented by clinicians who have had broad experience in this field. Finally, a program pertaining to methods of intravascular catheterization for the purpose of diagnosis will be presented.

The course has been arranged during the week immediately preceding the Annual Meeting of the American Medical Association in order that physicians from longer distances may combine the course with attendance at the A. M. A. Meeting. Hotel rooms may be occupied continuously through the two weeks' period.

Hotel Accommodations: In view of the fact that this course immediately precedes the Annual Meeting of the American Medical Association, and since that Association has reserved all possible rooms in San Francisco for the period of its meeting, it has been arranged to use the regular hotel reservation blank of the American Medical Association (as published in the JOURNAL of the American Medical Association, December 31, 1949), to be sent to Dr. William H. Rustad, Chairman, A. M. A. Hotel Committee, Room 200, 61 Grove St., San Francisco 2, Calif. Members of this course are assured of getting suitable hotel accommodations not only for the period of this course but for the A. M. A. Meeting, or for the course only, if desired. The College will provide all registrants with a copy of the reservation form to be filed with Dr. Rustad. The reservation form gives a list of all San Francisco hotels and a map showing their location and an outline of the rates.

Outline of Course

Monday, June 19.
A.M. Session.
8:50– 9:00 Welcome by Dr. Stacy R. Mettier.
Chairman, Dr. William J. Kerr

Cardiology

9:00– 9:30 Etiology of Arteriosclerosis.
Dr. Rinehart.
9:30–10:00 Essential Hypertension in Pregnancy.
Dr. Page.
10:10–10:40 Timing of Murmurs in Cardiovascular Diagnosis.
Dr. Kerr.

Pathologic Physiology of Congestive Failure

10:40–11:15 Hemodynamic Considerations.
Dr. Brown.
11:20–12:00 Disturbances of Water and Electrolyte Balance.
Dr. Hopper.
P.M. Session.
Chairman, Dr. John B. Lagen
1:30– 2:00 Contributions of Isotopes to Advance in Cardiology.
Dr. Lawrence.
2:00– 2:30 Abnormal Cardiac Mechanisms in Acute Infectious Diseases.
Dr. Brainerd.
2:40– 3:20 Value of Unipolar Leads in Location of Myocardial Infarction.
Dr. Sokolow.
3:30– 4:00 Anticoagulants in the Treatment of Myocardial Infarction.
Dr. Marple.
4:00– 4:30 Recent Advances in Therapy of Myocardial Infarction.
Dr. Sampson.

Tuesday, June 20.
A.M. Session.
Chairman, Dr. Stacy R. Mettier

Diseases of the Blood and Arthritis

9:00– 9:30 Vitamin B-12.
Dr. Mettier.
9:30–10:15 Interrelationship of ABO Blood Groups and Rh Immunization; Use of Hapten.
Dr. Lucia.
10:20–11:00 Newer Chemotherapeutic Agents of Use in Treatment of Lymphomas and Leukemias.
Dr. Bierman.
11:10–12:00 Clinico-pathological Conference.
Drs. Rinehart and Mettier.
P.M. Session.
Chairman, Dr. Ernest H. Falconer
1:30– 2:00 Etiology of Hodgkin's Disease.
Dr. Bostick.

2:00– 2:30 The Influence of the Endocrines on Hematopoiesis.
Dr. Leonard.
2:40– 3:10 Fragility of Blood Platelets.
Dr. Aggeler.
3:15– 3:45 Allergic Purpura.
Dr. Ellenhorn.
3:50– 4:20 Skeletal Lesions Accompanying Blood Dyscrasias.
Dr. Falconer.
4:20 Colored Film: The Effect of ACTH on Patients with Rheumatoid Arthritis.
Dr. Engleman.

Wednesday, June 21.
A.M. Session.

Chairman, Dr. Leslie L. Bennett

ENDOCRINOLOGY

9:00– 9:30 Urine Hormone Assays—Their Present Value in Clinical Practice.
Dr. Escamilla.
9:40–10:10 Physiological Aspects of Adrenal Insufficiency with Special Reference to the Electrolyte Disturbances.
Dr. Luetscher.
10:30–11:00 Metabolic Effects of Compound E (Cortisone).
Dr. Bennett.
11:10–11:40 Metabolic Effects of ACTH (pituitary adrenocorticotropic hormone).
Dr. Kinsell.

P.M. Session.

Chairman, Dr. Hans Lisser

1:30– 2:00 Clinical Use of Radioiodine in Thyroid Disease.
Dr. Dailey.
2:10– 2:40 Clinical Use of the Testosterones for Their Protein-Anabolic Effects.
Dr. Gordan.
3:00– 3:30 Simulated Endocrine Disorders.
Dr. Craig.
3:40– 4:10 Amenorrhea: A Problem for the Internist.
Dr. Goldberg.

Thursday, June 22.
A.M. Session.

Chairman, Dr. Theodore L. Althausen

GASTROINTESTINAL DISEASES

9:00– 9:25 Gastrointestinal Symptoms of Genito-urinary Origin.
Dr. Smith.
9:25– 9:50 Gastrointestinal Symptoms of Cardiovascular Origin.
Dr. Sokolow.
9:50–10:10 Cytological Examination of Gastric Washings.
Dr. Bothereau.
10:20–10:45 Suction Biopsy of the Gastric Mucosa.
Dr. Althausen.
10:45–11:10 Radicular Pain Simulating Abdominal Disease.
Dr. Hand.

11:15–11:35 Hiatus Hernia.
Dr. Dailey.
11:35–12:00 Lesions of the Mouth—A Demonstration of Colored Slides.
Dr. Graves.

P.M. Session.

Chairman, Dr. Elbridge J. Best

1:30– 2:30 Management of Prepyloric Lesions.
Dr. Wilbur.
2:40– 3:30 Clinical X-Ray and Laboratory Features of Hepatoma and Cholangioma of the Liver.
Dr. Lewis.
3:40– 4:30 Diagnosis and Treatment of Ulcerative Colitis.
Dr. Palmer.

Friday, June 23.

A.M. Session.

Chairman, Dr. Henry D. Brainerd

THE ANTIBIOTICS

9:00– 9:30 The Rôle of the Laboratory in the Management of Chemotherapy.
Dr. Jawetz.
9:40–10:10 Recent Advances in Antibacterial Therapy in Tuberculosis.
Dr. Hinshaw.
10:30–11:00 Therapy of Non-pneumonic Respiratory Infections.
Dr. Rantz.
11:10–11:40 Chemotherapy in Viral and Rickettsial Diseases.
Dr. Meiklejohn.
11:40–12:00 Chemotherapy in Bacterial Infections.
Dr. Brainerd.

P.M. Session.

Chairman, Dr. James Hopper, Jr.

1:30– 2:10 Angiography.
Dr. Miller.
2:15– 2:55 Electrokymography.
Dr. Nowak.
3:00– 3:40 Radiocardiography.
Dr. Dobson.
3:50– 4:30 Cardiac Catheterization.
Dr. Leeds.

Course No. 9, CLINICAL ASPECTS OF MALNUTRITION, Hospital de Enfermedades de la Nutrición, Mexico, D. F. Salvador Zubirán, M.D., F.A.C.P., Director. August 14–25, 1950. Fees: A.C.P. Members, $60.00; Non-members, $120.00.

Officers of Instruction

Director of the Course

SALVADOR ZUBIRÁN, M.D., F.A.C.P., Professor of Medicine, Graduate School, National University of Mexico; Professor of Clinical Medicine, National University of Mexico School of Medicine; Director, Hospital de Enfermedades de la Nutrición; Member, Academia Nacional de Medicina de México.

Guest Professors

GEORGE R. HERRMANN, M.D., F.A.C.P., Professor of Medicine, University of Texas School of Medicine, Galveston, Tex.

KARVER L. PUESTOW, M.D., F.A.C.P., Professor of Clinical Medicine, University of Wisconsin Medical School, Madison, Wis.

JOHN B. YOUMANS, M.D., F.A.C.P., Dean and Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

ENRIQUE AGUILAR, Dent. D., Professor of Clinical Dentistry, National University of Mexico School of Dentistry.

ALEJANDRO AGUIRRE, M.D., Associate Professor of Pediatrics, Graduate School, National University of Mexico; Head of Service, Hospital Infantil.

JOSÉ BÁEZ VILLASEÑOR, M.D., Associate Professor of Clinical Medicine, National University of Mexico School of Medicine; Department of Hematology, Hospital de Enfermedades de la Nutrición.

FRANCISCO BASSOLS, M.D., Professor of Radiology, National University of Mexico School of Medicine; Chief, Department of Radiology, Hospital de Enfermedades de la Nutrición.

JOSÉ CALVO DE LA TORRE, M.D., Director, Instituto de Nutriología; Professor of Parasitology, National University of Mexico School of Medicine.

IGNACIO CHÁVEZ, M.D., Sc.D., F.A.C.P., Professor of Medicine, Graduate School, National University of Mexico; Director, Instituto Nacional de Cardiología; Member, Academia Nacional de Medicina de México; Member, El Colegio Nacional de México.

RENÉ CRAVIOTO, Chemist; Chief, Laboratory of Bromatology, Instituto de Nutriología; Professor of Nutrition, Instituto Politécnico Nacional.

MARIO FUENTES, M.D., Professor of Clinical Psychiatry, National University of Mexico School of Medicine; Head of Service, Manicomio General Member, Academia Nacional de Medicina de México.

DEDERICO GÓMEZ, M.D., Professor of Pediatrics, Graduate School, National University of Mexico; Director, Hospital Infantil; Member, Academia Nacional de Medicina de México.

FRANCISCO GÓMEZ MONT, M.D., Associate Professor of Endocrinology, Graduate School, National University of Mexico; Department of Endocrinology, Hospital de Enfermedades de la Nutrición.

JULIO HERNÁNDEZ PENICHE, M.D., Consulting Physician in Neurology, Hospital de Enfermedades de la Nutrición.

ROBERTO LLAMAS, M.D., Professor of Clinical Endocrinology, National University of Mexico School of Medicine; Director, Instituto de Biología, National University of Mexico; Head of Service, Hospital de Enfermedades de la Nutrición; Member, Academia Nacional de Medicina de México.

PEDRO DANIEL MARTÍNEZ, M.D., Professor of Clinical Pediatrics, Graduate School, National University of Mexico; Assistant Director, Hospital Infantil.

JORGE MILLÁN GUTIÉRREZ, M.D., Consulting Physician in Dermatology, Hospital de Enfermedades de la Nutrición.

FRANCISCO DE P. MIRANDA, M.D., F.A.C.P., Professor of Endocrinology, National University of Mexico School of Medicine; Member, Academia Nacional de Medicina de México, A.C.P. Governor for México.

RAFAEL RODRÍGUEZ, M.D., Associate Professor of Endocrinology, National University of Mexico School of Medicine; Department of Endocrinology, Hospital de Enfermedades de la Nutrición.

EDMUNDO ROJAS, M.D., Head, Department of Pathology, Hospital de Enfermedades de la Nutrición.

MAXIMILIANO SALAS, M.D., Professor of Pathology, Escuela Médico Militar; Head, Department of Pathology, Hospital Infantil.

LUIS SÁNCHEZ MEDAL, M.D., Associate Professor of Clinical Medicine, National University of Mexico School of Medicine; Department of Hematology, Hospital de Enfermedades de la Nutrición.

BERNARDO SEPÚLVEDA, M.D., Professor of Gastroenterology, Graduate School, National University of Mexico; Head of Service, Hospital de Enfermedades de la Nutrición; Member, Academia Nacional de Medicina de México.

JOSÉ MARÍA DE LA VEGA, M.D., Chief, Outpatient Department, Hospital de Enfermedades de la Nutrición.

Associates

EDUARDO BARROSO, M.D., Department of Gastroenterology, Hospital de Enfermedades de la Nutrición.

LÁZARO BENAVIDES, M.D., Head Resident, Hospital Infantil.

JOAQUÍN CRAVIOTO, M.D., Nutritional Service, Hospital Infantil.

ROBERTO HERNÁNDEZ DE LA PORTILLA, M.D., Department of Gastroenterology, Hospital de Enfermedades de la Nutrición.

JORGE MAISTERRENA, M.D., Associate Professor of Endocrinology, National University of Mexico School of Medicine; Department of Endocrinology, Hospital de Enfermedades de la Nutrición.

RAFAEL RAMOS GALVÁN, M.D., Head of Service, Hospital Infantil.

This is an entirely new course on the College schedule. There is probably no institution or group of teachers so well qualified to give a thoroughly practical course in the subject of clinical aspects of malnutrition, because malnutrition is one of the gravest problems in Mexico. Assembled on the faculty will be outstanding authorities from Mexico, all of whom speak English, with two or more outstanding teachers from the United States.

The medical profession of the United States and Canada, interested in this subject, will have an opportunity to learn at first-hand the important strides being made in this field in Mexico. Furthermore, this opportunity will contribute much to the good professional relationships and acquaintanceships of the participating countries. College members, who have taken our postgraduate course in Cardiology in Mexico during 1948 and 1949, were amazed at the facilities and the plane of instruction offered in that country.

The course will cover the fundamental and practical problems of nutrition and should be superior to any course in this field previously offered by the College.

Mexico City is at such an elevation that the climate is delightful and comfortable, even in the midst of summer. There is so much of interest and attraction that the vacation features alone should attract a large number of registrants. Accommodations are available for wives and members of the family.

Entering Mexico: Air travel places Mexico City within reach of any section of the United States or Canada within practically one day. Thus many may prefer to travel by air rather than the longer route by train, although excellent train service is available.

The formalities of entry into and departure from Mexico are made very simple for the visitor. A "tourist card" shall be obtained from your nearest Mexican Consul. The American College of Physicians has the form of application available and a list of Mexican Consulates. As evidence of citizenship, either a birth or baptismal certificate, or an old passport, or a voter's registration card should be submitted with the application. The charge for the tourist card is $2.10, American currency, and checks should be made payable to the Mexican Consulate. Motorists require an auto permit issued by the Mexican Customs or by the border offices of the Mexican Automobile Association.

Train passengers are not obligated to leave their Pullmans unless they have trunks to be examined. Steamship and air passengers go through the most simple formalities at border, port, airport, or at destination. A visitor may leave Mexico either by port of entry or by any other port. The tourist card must be returned to the border authorities for cancellation.

Money and Rate of Exchange: The "peso" is Mexico's monetary unit. Centavos correspond to cents, and the peso equals 100 centavos. Travelers' checks are accepted anywhere. The U. S. dollar is equal to approximately $8.60 Mexican currency. At the border the best plan is to exchange only enough money to suffice until you reach your destination, where bank rates are likely to be more favorable.

Language: A knowledge of Spanish is by no means necessary, although it is helpful. The course will be conducted in English. Everywhere in hotels, restaurants, and stores, there are employees who speak English well. For the convenience of the visitor, the Mexico City Police Force has a special corps of policemen who speak foreign tongues. Look for your flag on an officer's sleeve—he will gladly answer your questions in English.

Immunization Information: The Mexican Government requires nothing from the American citizen, but the American Government requires a certificate of vaccination from American tourists returning home from abroad. In the absence of unusual outbreaks of disease, the United States has no immunization requirements for persons leaving the United States, except as may be required for military personnel and dependents. The Foreign Quarantine Regulations of the United States, however, require that all persons, both American citizens and nationals of other countries, prior to admission to the United States from abroad, present a certificate showing satisfactory evidence of vaccination against smallpox within three years prior to arrival or evidence of a previous attack of smallpox.

Hotel Headquarters: Hotel Reforma, Pasea de la Reforma Boulevard, Mexico, D. F. Rates: Single, 45 pesos; double, 55 pesos (approximately $5.22 and $6.37, respectively).

Aguirre's Guest Tours: Mr. Enrique Burmeister, General Manager, Cinco de Mayo No. 18, Mexico, D. F., has arranged a special official program of entertainment and sight-seeing including several half-day inspection tours of Mexico City, the Pyramids, Xochimilco, Desert of the Lions, Tepotzotlán and other special points of interest, and a week-end tour to Cuernavaca and Taxco. Competent guides, modern passenger sedans, and accommodations at the better class of hotels and restaurants are provided. In fact, Aguirre's Guest Tours will make all of one's arrangements in Mexico, including hotel accommodations and reservations for all of their tours, including transfers from and to hotels and stations; their all-inclusive rate being $198.00 (U. S.) per person sharing twin-bedded room with private bath at Hotel Reforma, or $223.50 (U. S.) per person for single room with private bath. Those interested should write to Aguirre's Guest Tours for full details, identifying themselves with the American College of Physicians and this course.

Outline of Course

(Programs will conclude daily at 1:00 P.M.)

Sunday, August 13.

10:00 A.M. Cocktail-lunch offered by Dr. Salvador Zubirán at his home in San Jerónimo.

Monday, August 14.

9:00 A.M. Introduction to the Course.
Dr. Salvador Zubirán.

9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:30 A.M. The Rôle of Food and Disorders of Metabolism in Cardiovascular Disease Processes.
Dr. George R. Herrmann.

Tuesday, August 15.
9:00 A.M. Hypoproteinosis.
Dr. Francisco de P. Miranda.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:00 A.M. Studies of the Food Habits of Our Population, as Compared with American Standards.
Dr. José Calvo de la Torre.

Wednesday, August 16.

SYMPOSIUM ON NUTRITIONAL FACTORS IN THE ETIOLOGY AND TREATMENT OF HEPATIC CIRRHOSIS

Lectures, discussions and presentation of clinical cases.
Drs. Bernardo Sepúlveda, Edmundo Rojas and Associates.

9:00 A.M. Lectures and discussions.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:30 A.M. Lectures and discussions.
12:00 Noon. Lectures and discussions.

Thursday, August 17.
9:00 A.M. Clinical Aspects of Malnutrition in Cardiovascular Diseases.
Dr. Ignacio Chávez.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:30 A.M. Skin Lesions in Nutritional Deficiencies.
Dr. Jorge Millán Gutiérrez.
12:00 Noon. Nutritive Value of Our Foods.
Dr. René Cravioto.

Friday, August 18.
9:00 A.M. Psychiatric Manifestations in Nutritional Deficiencies.
Dr. Mario Fuentes.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:30 A.M. Neurologic Complications in the Deficiency States.
Dr. Julio Hernández Peniche.
12:00 Noon. Dental Lesions in Malnutrition.
Dr. Enrique Aguilar.

Monday, August 21.

SYMPOSIUM ON ENDOCRINE MANIFESTATIONS IN MALNUTRITION

Lectures, discussions and presentation of clinical cases.
Drs. Roberto Llamas, Francisco Gómez Mont and Rafael Rodríguez.

9:00 A.M. Lectures and discussions.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.

11:30 A.M. Lectures and discussions.
12:00 Noon. Lectures and discussions.

Tuesday, August 22.

SYMPOSIUM ON CLINICAL ASPECTS OF MALNUTRITION IN PEDIATRICS

Lectures, discussions and presentation of clinical cases.
Drs. Frederico Gómez, Pedro Daniel Martínez, Alejandro Aguirre, Maximiliano Salas and Associates.

9:00 A.M. Lectures and discussions.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:30 A.M. Lectures and discussions.
12:00 Noon. Lectures and discussions.

Wednesday, August 23.

SYMPOSIUM ON ANEMIAS DUE TO NUTRITIONAL DEFICIENCIES

Lectures, discussions and presentation of clinical cases.
Drs. José Báez Villaseñor and Luis Sánchez Medal.

9:00 A.M. Lectures and discussions.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:30 A.M. Lectures and discussions.

Thursday, August 24.

9:00 A.M. The Clinical Evaluation of Nutritional Deficiency States.
Dr. John B. Youmans.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:00 A.M. Gastrointestinal Manifestations in Deficiency States.
Drs. José María de la Vega and Francisco Bassols.

Friday, August 25.

9:00 A.M. Nutritional Problems in Diabetes.
Dr. Salvador Zubirán.
9:40 A.M. Rounds on the Wards.
Presentation of Clinical Cases.
11:30 A.M. Nutritional Aspects of Idiopathic Ulcerative Colitis.
Dr. Karver L. Puestow.
8:00 P.M. Banquet.
Address by Dr. Karver L. Puestow.

During a refresher course for physicians on the diagnosis of neoplastic disease, under the auspices of the California Cancer Commissions, held in the auditorium of the Los Angeles County Hospital, February 19–20, Dr. Howard R. Bierman (Associate), San Francisco, presented a paper on "Malignant Lesions of the Blood and Lymph Nodes."

Among those presenting papers at the Annual Heart Day of the Michigan Heart Association, in Detroit on March 11, were Dr. Irvine H. Page, F.A.C.P., Cleveland, who spoke on Hypertension, and Dr. Louis N. Katz, F.A.C.P., Chicago, whose subject was Arteriosclerosis.

The promotion of Capt. Frederick C. Greaves, F.A.C.P., Commanding Officer, Naval Hospital, Bethesda, Md., to the rank of Rear Admiral has been approved by President Truman.

Dr. George Piness, F.A.C.P., Associate Professor of Medicine at the University of Southern California School of Medicine, was a guest speaker at the Pediatric Conference held March 15–16, at the University of Arkansas School of Medicine, Little Rock.

Dr. Max M. Strumia, F.A.C.P., Associate Professor of Medicine, University of Pennsylvania School of Medicine, has been elected President of American Medical Relief for Italy and Pennsylvania, Inc.

Dr. Reginald C. Edson, F.A.C.P., Hartford, Director of Tuberculosis Control, Connecticut State Tuberculosis Commission, has been elected Secretary-Treasurer of the newly established Connecticut Trudeau Society, which is affiliated with the American Trudeau Society.

Among various medical leaders testifying before the Senate Committee on Finance during public hearings on amendment of the Social Security Act were Dr. James E. Paullin, M.A.C.P., Atlanta, Ga.; Dr. R. L. Sensenich, F.A.C.P., South Bend, Ind.; and Dr. Bradford J. Murphey, F.A.C.P., Denver, Colo.

Dr. Theodore R. Van Dellen, F.A.C.P., Assistant Dean of Northwestern University Medical School, Chicago, has been promoted to Associate Professor of Medicine.

Dr. Paul D. White, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School, was one of the speakers at a two-day Public Health Conference sponsored by the West Virginia University School of Medicine, Morgantown, March 31 and April 1. Dr. Leonard A. Scheele, F.A.C.P., Surgeon General, U. S. Public Health Service, was the speaker at the Friday evening banquet, and Dr. Thomas Parran, F.A.C.P., Dean of the School of Public Health, University of Pittsburgh, was the speaker at the luncheon on Saturday.

Dr. Irving S. Wright, F.A.C.P., New York City, will be a guest speaker at the 28th Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, to be held October 2–5, 1950, in Kansas City, Mo.

Dr. Archibald L. Hoyne, F.A.C.P., resigned as Medical Superintendent of the Municipal Contagious Disease Hospital, Chicago, at the close of December, 1949. Dr. Hoyne had been medical director for more than thirty years.

Dr. Robert H. Flinn, F.A.C.P., is the newly appointed chief of Health Emergency Planning for the U. S. Public Health Service, succeeding Dr. Norvin G. Kiefer, now on assignment to the National Security Resources Board as director of the Health Resources Division.

The Health Emergency Planning Unit was established in the Public Health Service in 1948. Its functions are to plan for more comprehensive public health catastrophe services in answer to peace time emergency requests from states and to coöperate with the National Security Resources Board and other governmental and voluntary agencies in civil defense planning.

Heretofore, since 1948, Dr. Flinn has been directing the Medical Branch of the Federal Employee Health Division.

Dr. Martin G. Goldner, F.A.C.P., Director of Medical Research, Chief of the Gastrointestinal and Metabolism Section of the Veterans Administration Hospital, Fort Logan, Colo., and Assistant Clinical Professor at the University of Colorado Medical Center, has been appointed Chief of Medicine at the newly established Fort Hamilton Veterans Administration Hospital, Brooklyn, N. Y., which as a teaching institution is affiliated with the Long Island College of Medicine.

Dr. David W. Kramer, F.A.C.P., has presented the College Library with a copy of his book, "Peripheral Vascular Diseases," published by F. A. Davis Company. The College Library, which is a memorial to the Fellows of the College, is growing in value and sentiment as more and more Fellows are presenting copies of their books to it.

The American Physicians Art Association announces its twelfth art exhibition in conjunction with the American Medical Association Convention at the San Francisco Auditorium June 26–30, 1950. Any physician whose hobby is fine or applied arts can exhibit by becoming a member of the American Physicians Art Association and applying for entry blanks and shipping labels to the secretary, F. H. Redewill, M.D., 526 Flood Bldg., San Francisco 2, Calif. Many trophies will be awarded to advanced artists as well as beginners. The purpose of the Association is to encourage physicians to take up art in some form as an avocation.

An honorary degree of Doctor of Science was conferred upon Dr. Leonard A. Scheele, F.A.C.P., Surgeon General, U. S. Public Health Service, during Wayne University's midyear commencement exercises held February 2, in the Masonic Temple at Detroit, Mich.

Dr. David D. Henry, President of Wayne University, conferred the degree and presented Dr. Scheele with a citation summarizing the achievements for which he is recognized.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., will speak on "Errors of Priority Credit in Medicine" at the annual meeting of the American Association of the History of Medicine to be held in Boston, May 22, 1950.

Dr. Carl A. Johnson (Associate), Chicago, has been appointed to the Faculty of the University of Illinois College of Medicine with the rank of Assistant Professor in Clinical Science.

Dr. Johnson has held an appointment at Northwestern University Medical School since 1930 and is attending physician at St. Luke's Hospital.

Dr. Stanley W. Olson, Assistant Director of the Mayo Foundation, Rochester, Minn., was recently appointed Dean of the University of Illinois College of Medicine. He assumed his duties on April 1, succeeding Dr. John B. Youmans, F.A.C.P., who has accepted the Deanship of Medicine at Vanderbilt University, Nashville, Tenn. Dr. Olson will serve as Medical Director of the University's Research and Educational Hospitals.

The University of Pittsburgh School of Medicine gave an intensive postgraduate course in gastroenterology April 3–6, 1950. The course was organized under the plan of symposia, including the following: stomach and duodenum; intestines; liver; biliary tract and pancreas; esophagus. The material was presented through illustrated lectures at the Falk Clinic at the School of Medicine. The last afternoon of the course was devoted to case presentation and discussion at the Veterans Administration Hospital, Aspinwall, Pa. Enrollment was limited to 35 and the tuition fee was $35.00.

Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Editor of the Journal of the Oklahoma State Medical Association, was recently honored by the National Association for the Prevention of Tuberculosis of Great Britain by being asked to serve on the Editorial Board of the "Tuberculosis Index," which is the Association's bibliography of everything published about tuberculosis, including abstracts of the current literature.

Dr. Robert A. Matthews, F.A.C.P., formerly of Philadelphia, has recently been appointed Professor of Psychiatry and Head of the Department of Neuropsychiatry at Louisiana State University School of Medicine, New Orleans.

At a dinner held on February 16, marking the twenty-fifth anniversary of the Colorado Psychopathic Hospital and honoring Dr. Franklin G. Ebaugh, F.A.C.P., Denver, who has been director of the hospital since its founding, the Ebaugh Foundation of the University of Colorado Medical Center presented a fund to the university to finance a yearly research fellowship in Psychiatry.

Dr. Edward F. Rosenberg, F.A.C.P., Chicago, Chief of the Arthritis Clinic, Michael Reese Hospital, was recently appointed Assistant Professor of Medicine at the Chicago Medical School.

Columbia University School of Public Health in coöperation with the Bureau of Nutrition and Laboratories of the New York City Department of Health will make fellowships in clinical nutrition available to physicians who intend to use the knowledge acquired in public service. These fellowships will consist of one year's training in the School of Public Health, with elective studies in nutrition, leading to the degree of Master of Public Health. Second and third years will consist of clinical investigation and research. Fellowships will become available either July 1 or September 1 with a stipend of $3,600 per year, or more, depending on previous training and the needs and requirements of the individual. Inquiries should be addressed to Dr. Harold W. Brown, School of Public Health, Columbia University, New York 32, N. Y.

Dr. Richard W. Vilter, F.A.C.P., Associate Professor of Medicine and Assistant Dean of the University of Cincinnati College of Medicine, has just received a $5,000 grant for research from the National Vitamin Foundation, Inc. Dr. Vilter will study the human body's need for Pyridoxine (Vitamin B_6).

Dr. James A. Halsted, F.A.C.P., Boston, has resigned as Chief of the Medical Service of the Faulkner Hospital in order to accept a full-time position as Section Chief in the Wadsworth Veterans Administration Hospital, Los Angeles, Calif.

Dr. Mayer A. Green, F.A.C.P., Pittsburgh, Pa., presented a paper entitled "Herpes Gestationis" at the Sixth Annual Session of the American College of Allergists held January 15–18 in St. Louis, Mo.

Dr. Paul B. Beeson, F.A.C.P., Atlanta, Ga., and Dr. Jerome W. Conn, F.A.C.P., Ann Arbor, Mich., were among the guest speakers at the Nineteenth Annual Spring Clinical Conference of the Dallas Southern Clinical Society held March 13–16 in Dallas, Tex.

Dr. F. William Sunderman, F.A.C.P., of Atlanta, Ga., has presented the College Library with a copy of the 1949 edition of his book, "Normal Values in Clinical Medicine" (with Frederick Boerner), published by W. B. Saunders Company.

At a joint meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia on March 8, 1950, Dr. Joseph L. Hollander, F.A.C.P., and Dr. John Lansbury, F.A.C.P., both of Philadelphia, presented papers in connection with the Symposium on Rheumatoid Arthritis. Dr. Hollander was Chairman of the Symposium.

OBITUARIES

DR. WILFRED E. CHAMBERS

Dr. Wilfred E. Chambers, M.D., F.A.C.P., died in the Veterans Administration Hospital, Indianapolis, Ind., on September 26, 1949.

Dr. Chambers was born in Chapeltown, England, August 25, 1874. He came to the United States at the age of fourteen and became a naturalized citizen in Oakland, Calif., in 1898. He graduated with degree of M.D. from the College of Physicians and Surgeons in San Francisco in 1906, and in the following year served his internship and later his residency at the San Francisco City and County Hospital. In 1908, Dr. Chambers was appointed acting surgeon in the United States Public Health and Marine Service with particular duties in regard to inspection and fumigation in control of bubonic plague. In 1909 he took a postgraduate course at the New York University and in 1910 settled down to the general practice of medicine in Oakland, Calif.

Dr. Chambers' practice was interrupted in 1916 when he enlisted in the United States Army as Captain in the Medical Corps and served on the Mexican Border. Immediately following this service, Dr. Chambers entered World War I in the Medical Corps. After the war, he was appointed Chief Medical Officer of Veterans Foreign Relations, Washington, D. C. In 1922 Dr. Chambers returned to his work with the United States Public Health Service and was appointed Chief Surgeon of the hospital at Arrowhead Springs, Calif. From there his work was transferred to the Veterans Hospital, Excelsior Springs, Mo., in 1924. There followed subsequent changes of location—in 1927 he was put in charge of the Veterans Hospital, Kansas City, Mo.; in 1933, Chief Medical Officer, Soldiers Home, Leavenworth, Kans.; in 1934, Veterans Hospital, Whipple, Ariz.; and finally in 1937, Chief Medical Officer, Veterans Hospital, Indianapolis, Ind. Dr. Chambers remained at his last assignment for seven years till his retirement at the age of seventy.

Dr. Chambers was a man of wide interest as is shown by his extensive memberships in many organizations. Aside from his medical associations he was a member of the Murat Temple and Scottish Rite, Indianapolis; Orient Lodge (A.F. and A.M.), Kansas City, Mo.; Alpha Kappa Kappa; Officers Reserve Corps; 40 & 8 Voiture, Prescott, Ariz.; American Legion, National Cathedral, Washington, D. C.; Military Order of the World War. He had been a Fellow of the American College of Physicians since 1928.

Dr. Chambers practiced medicine in California, Nevada, Missouri and Indiana, and his contacts with medical organizations in many other locations must have given him an unusually good vision of the field. He will be greatly missed by all his appreciative friends.

J. O. RITCHEY, M.D., F.A.C.P.,
Governor for Indiana

DR. THOMAS ADDIS

Thomas Addis was born in Edinburgh on July 27, 1881. He received the M.B. degree from that city's medical school in 1905; after three years of hospital training in Edinburgh, Gloucester and Bristol he became an M.D. and M.R.C.P. in 1908. The tenure of a Carnegie Scholarship and Fellowship he spent in Berlin and Heidelberg in 1909–10, then returned to Edinburgh to the Laboratory of the Royal College of Physicians. In 1911 he came to Stanford University School of Medicine, called by the late Dean Ray Lyman Wilbur at the advice of Sir Clifford Allbutt. He married Elesa Bolton Partridge in 1913, and is survived by his widow, their two daughters and six granddaughters. But for leaves of absence he remained at Stanford throughout his career, as Professor of Medicine from 1921 and Professor Emeritus from 1946.

From the start he was a laboratory man, scholar and scientist. But he was never

a cold scientist; in all of his work there ran one thread of deep friendship and concern for his patients and another by which he sought to tie his hard-won knowledge of fundamental science to the daily practice of medicine.

Before he had been long at Stanford, his genius for research became evident, and he soon managed to minimize routine laboratory work and formal teaching in required courses. Yet his influence upon medical students and doctors here and abroad was considerable, for he was a really great teacher. Saturdays and Sundays, as well as week-days, found him in the laboratory. He enjoyed this sort of labor, and in the next forty years did much more than enough hard work to permit publication of over 120 papers and two books.

When Addis began his work in clinical laboratories, it was possible to do little more with patients than to study their blood, urine and stools. He began with the blood and its coagulation while a Carnegie Scholar and Fellow in Germany, and published nine papers from 1908 to 1911 which dealt with hemophilia and which are still quoted today. At Stanford in 1913, he wrote on diabetes mellitus; of this short series, one study on clinical methods for estimating the degree of acidosis indicated that his desire to transmute science to practice was already present. With Dr. Wilbur, he published three papers on urobilin and hemoglobin pigment metabolism; these also became classics. Away from the laboratory as a Captain in the U. S. Army Medical Corps in 1918–19, he made basic observations upon such simple things as pulse rate and blood pressure. With these exceptions, the remainder of his medical career dealt entirely with the kidney and Bright's disease.

These studies began in 1916 when, with Dr. George Barnett, he first wrote on the excretion of urea. The next two years saw the fruits of much labor in the form of a score of publications on urea excretion and the regulation of renal activity. This was the start of modern renal physiology, the foundation of the current concept of clearances (as Addis put it, so much blood was "freed" of urea in unit time). This sequence was continued, shortly after his return from the Army and promotion in 1921 to Professor of Medicine, by a dozen papers upon the same theme. These 30-odd articles all bore on the physiology of the normal kidney, that of the rat, rabbit and dog, but particularly of man. They yielded a method for the determination of how much renal tissue was present in a given individual, or conversely, how much had been destroyed by disease. Addis then turned to the neglected art of looking at the urinary sediment for clues as to the nature of that disease; by devising a simple but quantitative method for dealing with casts, blood cells and kidney cells he was soon able to add to the certainty of diagnosis and to gauge the severity of the process. This was first briefly described (1922) in the California State Journal of Medicine, and was followed three years later by his classic work, in the Journal of the American Medical Association, on the Clinical Classification of Bright's Diseases. He did not overlook the effects of such things as exercise and diet upon the number of casts and other formed elements, which he carefully showed were present together with minute amounts of protein in the urine of normal individuals.

Such researches allowed, for the first time, an accurate estimate of the nature, intensity and extent of the renal lesion in patients with the formerly vague "Bright's disease." This was the subject upon which Dr. Addis spoke when he was honored by his selection to deliver the Harvey Lecture in 1928. Also in that year he won the Gibbs prize for research in disorders of the kidney, and he spent the year as Visiting Fellow at the Rockefeller Institute. Further recognition came when he was invited to give the Thayer Lectures in 1931, following his term as president of the American Society for Clinical Investigation. Judged by the acclaim and worldwide recognition he had just won, the career of Dr. Addis might be said to have reached its peak; in this period, too, he found time to complete and publish with Dr. Jean Oliver their monumental book, The Renal Lesion in Bright's Disease.

Thus far his published work bore chiefly upon the physiology of normal kidneys and the more precise diagnosis of the disturbance in the case of diseased kidneys. But for Addis there were no "cases" but rather living beings, his friends who were sick and required treatment; all that had gone before was only the logical basis for rational therapy. He had for some time come to believe that the diseased kidney should be put to rest in order to promote healing; accordingly, a typically extensive study was begun of the effects of work load not only upon the kidney but also upon the heart, lungs and intestines (from 1932). Dietetic variations, as they altered the kidneys, were examined as early as 1926. The interrelationships between renal work, urea excretion and dietary protein were thoroughly explored, with extension of research to the many aspects of protein in various organs of the body, in a score of papers from 1936 to 1940. By then there had been published four articles which were concerned specifically with the therapeutic principle of rest for the ailing kidney.

Continuing these basic studies, which were temporarily adapted toward war work as yet virtually unpublished, Addis became increasingly occupied with the need for simplifying the laboratory methods of examining patients with renal diseases so that the scientific knowledge which he had won with such industry and exactness could be applied economically by all physicians in their practice of medicine. Achievement of this end required still more work in the laboratory, on patients and rats alike, and this was in full progress when Dr. Addis became Emeritus Professor of Medicine in 1946. He stayed on two years more, leaving Stanford in 1948 a few months after the publication of his *Glomerular Nephritis: Diagnosis and Treatment*. It is in this small book that his labor of three decades reached its climax; here is the exposition of his practical management of patients with kidney disease, based on the principle of reducing the work load upon the ailing kidney.

Nor did he rest even then. One of the chief and simplest signs of trouble with the kidneys is proteinuria, and now Addis turned to methods for its study. Finding space and assistance at the Cedars of Lebanon Research Institute in Los Angeles, he moved there and was at work as usual when the illness began that was to end in his death on June 4, 1949.

Some of the honors which he received in recognition for his distinguished career have already been mentioned. Perhaps the most fitting was the Cullen Prize, given to Dr. Addis in 1942 by the Royal College of Physicians of Edinburgh—the Prize is awarded every four years to the man who has made the "greatest contribution to practical medicine."

DR. EDWARD WALDEMAR ANDERSON

Dr. Edward Waldemar Anderson, F.A.C.P., died in Des Moines, Iowa, September 5, 1949, of cerebral hemorrhage after an illness of three years.

He was born at Marion, Iowa, November 11, 1898. He received his M.D. degree in 1923 at the State University of Iowa College of Medicine. He served as Fellow at the Mayo Foundation, 1925–1927, and as First Assistant in Medicine at the Mayo Clinic from 1927–1930. He was an instructor in Pathology at Dartmouth Medical School, and Internist at Mary Hitchcock Memorial Hospital, Hanover, New Hampshire, 1930–31. He moved to Des Moines, Iowa, in 1932 where he was a member of the staff of Mercy, Iowa Methodist and Broadlawns General Hospitals. Dr. Anderson was Lieutenant Commander, Medical Corps, U. S. Naval Reserve; Diplomate, American Board of Internal Medicine; and Fellow of the American College of Physicians since 1932. In addition to the duties of his private practice he was an Assistant Medical Director for the Central Life Assurance Society of Iowa, and Physician to the Des Moines Public School System.

Dr. Anderson was a well trained, able internist, whose capable work was respected by all who knew him.

B. F. Wolverton, M.D., F.A.C.P.,
Governor for Iowa

DR. STAIGE DAVIS BLACKFORD

Staige Davis Blackford, B.S., M.D., F.A.C.P., Charlottesville, Va., was born December 28, 1898, and died of coronary thrombosis at Charlottesville, Va., on July 17, 1949.

He received both his academic and medical training at the University of Virginia. He did postgraduate work at the Mayo Clinic, Duke University and Massachusetts General Hospital. He had been successively Assistant Professor of Medicine, Associate Professor of Medicine and Professor of the Practice of Medicine in the University of Virginia. For many years he had been on the medical staff of the University of Virginia Hospital.

Dr. Blackford was the author of numerous articles on tularemia, gall bladder disease, spontaneous pneumothorax and other topics. He was keenly interested in both undergraduate and postgraduate medical education. As chairman of the Medical School Committee on Postgraduate Education he organized many refresher courses for practicing physicians. He was the first editor of the University's Medical Alumni Bulletin and he was the first chairman of the Clinical Staff of the University Hospital.

He was a member of the Albemarle County Medical Society, the Virginia State Medical Association, the American Medical Association, the American Clinical and Climatological Association, and had been a Fellow of the American College of Physicians since 1941. He served during World War I with the University of Virginia section of the Army Ambulance Service. He was decorated with the Croix de Guerre. When the United States entered World War II he organized the University of Virginia Hospital Unit which became the Eighth Evacuation Hospital. Dr. Blackford served as its Chief of Medicine for more than 30 months in North Africa and Italy. He was decorated with the Legion of Merit and the Medal of French Morocco. On his release from active duty, he held the rank of Colonel.

As an educator and a soldier in two wars, his contributions to the University, the State, and the Country he loved, were outstanding. But more remarkable than his tangible accomplishments was his unique personality. His unusual charm, wit and searching mind made him a peerless companion. His frankness and intellectual honesty made him a valued critic. His wide vision made him a trusted counsellor. His humanity, kindness, and unusual personal magnetism endeared him to many. To all of these his untimely death brought a feeling of genuine sorrow and irreplaceable personal loss.

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DR. SIGMUND SAMUEL GREENBAUM

Sigmund Samuel Greenbaum, M.D., F.A.C.P., was born at Philadelphia, March 17, 1890, and died October 3, 1949. He graduated from Jefferson Medical College in 1913, and thereafter did postgraduate work at the University of Paris. He was Professor of Clinical Dermatology and Syphilology at the University of Pennsylvania Graduate School of Medicine from 1935, forward; Attending Dermatologist, Philadelphia General Hospital, 1922, forward; Dermatologist, Graduate Hospital of the University of Pennsylvania; Dermatologist to Medical Advisory Board No. 1, Pennsylvania Selective Service, during World War II; Lecturer on Skin and Social Diseases, Philadelphia Occupational School of Therapy; Consulting Dermatologist, Eagleville Sanitarium and Camden General Hospital; Fellow in Research, Institute of Cutaneous Medicine; Director, Bankers Securities Corporation, Trustee, National Agricultural College.

Dr. Greenbaum served during World War I in the Medical Corps of the U. S. Army. He was co-author of a textbook, "Diseases of the Mouth and Their Treatment," published by Lea and Febiger; author, "Dermatology and General Practice," published by F. A. Davis Company; and he published a host of other articles.

Dr. Greenbaum was a diplomate of the American Board of Dermatology and Syphilology, and had been a Fellow of the American College of Physicians since 1932. His death was due to coronary occlusion.

DR. MARTIN ALVIN MORTENSEN

Martin Alvin Mortensen, M.D., F.A.C.P., Santa Monica, Calif., died on November 8, 1949, at the age of 77. He was born at Westfield, Wis., in 1871, and graduated in medicine at the University of Michigan in 1899. He did postgraduate work at the University of Austria, at the London Hospital under Sir James MacKenzie, and at the Charité Hospital in France. For many years he was active on the staff of the Battle Creek Sanitarium at Battle Creek, Mich. During the recent war he moved to Santa Monica, Calif., where for a time he engaged in the practice of internal medicine and cardiology, but in more recent months had completely retired.

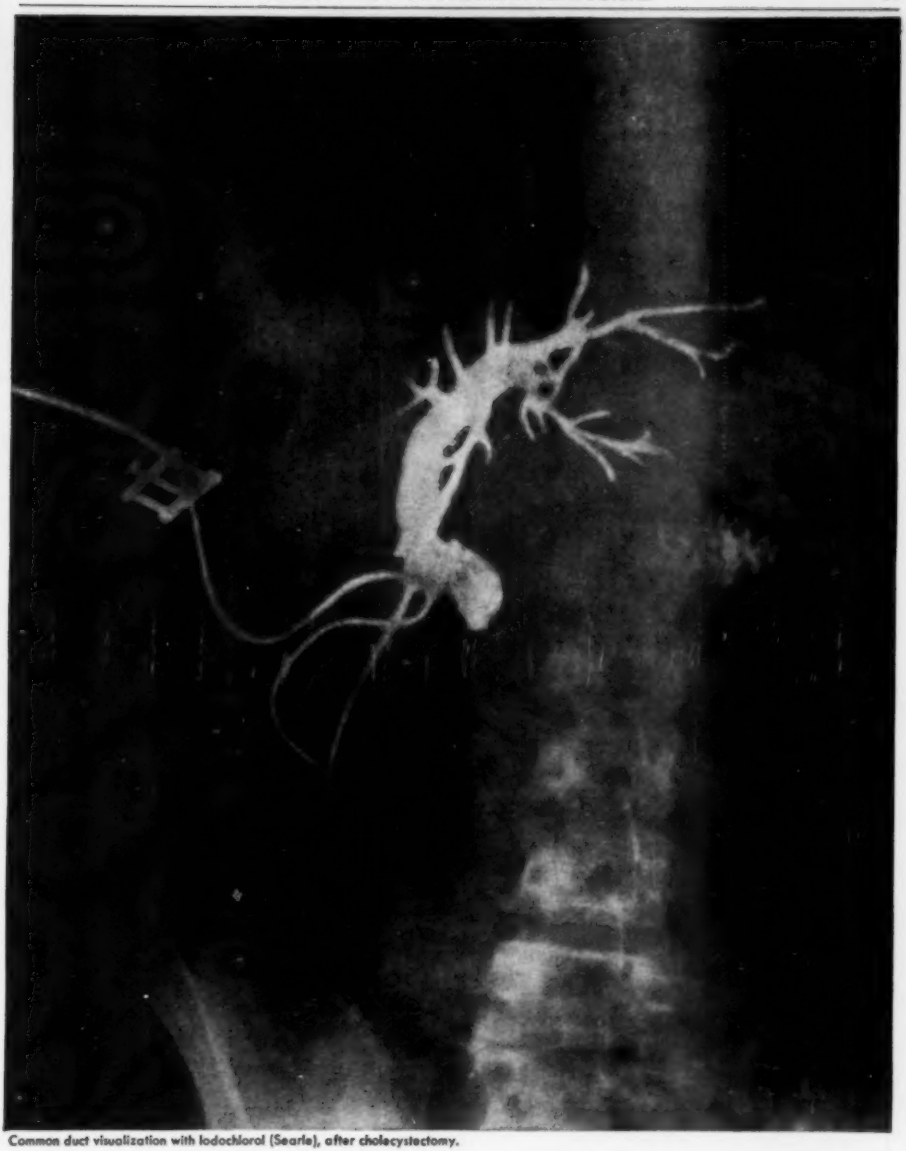
DR. ROBERT EWART RAMSAY

Robert Ewart Ramsay, A.B., A.M., M.D., F.A.C.P., of Pasadena, Calif., died September 19, 1949, at the age of 73.

Dr. Ramsay was born at Glasgow, Scotland, September 18, 1876. He came to the United States at an early age, received his A.B. degree in 1899 and his A.M. degree in 1907 from Harvard University. He graduated in medicine in 1917 from the University of Southern California School of Medicine, and thereafter interned at the Children's Hospital, Boston. Following this, he served a residency in pediatrics at the Infants Hospital, Boston.

Dr. Ramsay for many years was a member of the faculty, Associate Professor and later Professor of Pediatrics, College of Medical Evangelists, Los Angeles. He served on the staff of the Huntington Memorial Hospital and St. Luke Hospital. At one time, he was Attending Pediatrician, Los Angeles County and Collis P. and Howard Huntington Memorial Hospital; member, Board of Directors, California Babies Hospital; Consulting Pediatrician, Pasadena Public Schools.

Dr. Ramsay was a Diplomate of the American Board of Pediatrics; Fellow of the American Academy of Pediatrics; Fellow of the American College of Physicians since 1928; former Secretary and former President, Southwestern Pediatric Society; former Councillor, Los Angeles County Medical Association; former Vice President, Southern California Medical Association; and a Fellow of the American Medical Association.



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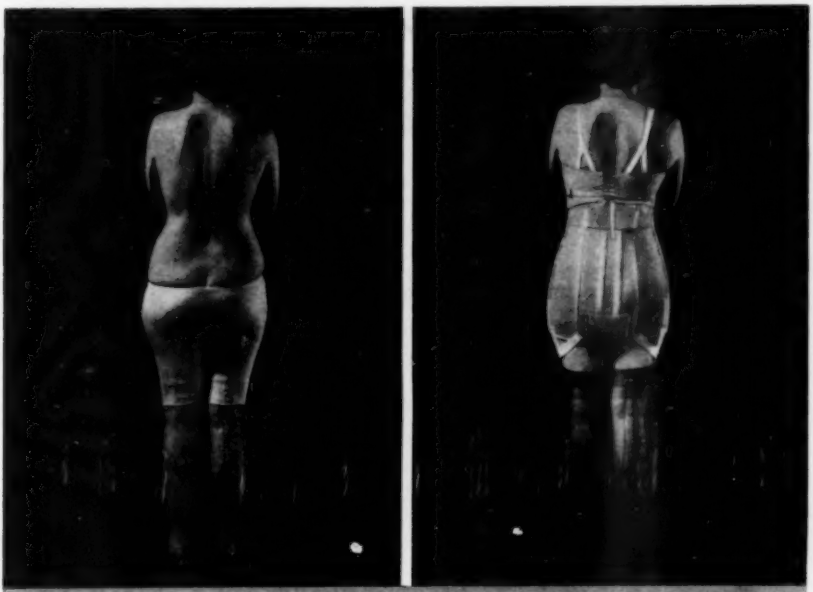

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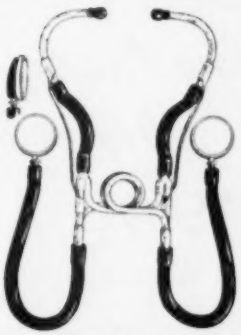

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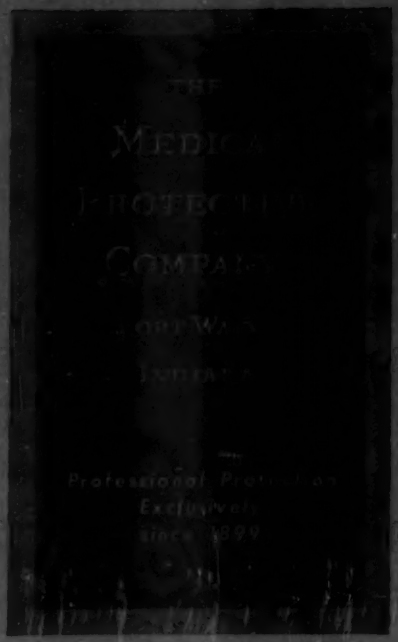

INDEX TO ADVERTISERS

April, 1950

Abbott Laboratories 31
Ames Company, Inc. 10
Appleton-Century-Crofts, Inc. ..Second Cover
Armour Laboratories 16
Bilhuber-Knoll Corp. 4
Burroughs Wellcome & Co. (U.S.A.) Inc. 13, 21
Cambridge Instrument Co., Inc. 5
S. H. Camp and Company 41
Central Pharmacal Co., The 29
Chicago Dietetic Supply House, Inc. 43
Chilcott Laboratories 7
Ciba Pharmaceutical Products, Inc. 6
Davies, Rose & Company, Limited 8
Denver Chemical Mfg. Co., Inc., The ... 32
Devereux Schools 43
Dietene Company, The 18
C. B. Fleet Co., Inc. 26
Flint, Eaton & Company 27
General Electric X-Ray Corporation 12
Hille Laboratories 22
Paul B. Hoeber, Inc. 3
Hospital Bedlight Company 40
Ives-Cameron Company, Inc. 20
Kelley-Koett Manufacturing Co., The 30
LaMotte Chemical Products Company ... 40
Eli Lilly and Company 9
Macmillan Company, The 1
Medical Protective Company, The ..... Third Cover
Merck & Co., Inc. 17
Nepera Chemical Co., Inc. 28
Oxford University Press, Inc. 4
A. J. Parker Company 34
Sanborn Company 36
Schenley Laboratories, Inc. 11
Schering Corporation 15
G. D. Searle & Co. 39
Sharp & Dohme 38
Smith, Kline & French Laboratories 23
University of California 43
Upjohn Company, The 37
U. S. Vitamin Corporation 14
Varick Pharmacal Co., Inc. 35
Winder Company, The 24
White Laboratories, Inc. 33
Williams & Wilkins Company, The 2
Winthrop-Stearns, Inc. 25
Woodward Medical Personnel Bureau 44
Wyeth Incorporated 19

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Official Periodical of the American College of Physicians

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital, Baltimore 1, Md.

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

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